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AUREOMYCIN IN THE PROPHYLAXIS OF RHEUMATIC FEVER*

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DESPITE recent progress, the prevention of rheumatic fever remains a challenging problem. The investigation of this subject is made difficult by the lack of basic knowledge concerning the disease itself.[1] Rheumatic fever is widely recognized as a frequent and potentially serious condition; yet its actual incidence cannot be accurately determined.[2] Frequently, the clinical picture is quite atypical: there may be no arthritis or arthralgia; and the disease may be extremely severe or very mild. No precise diagnostic procedure is available.[3] Doubtless, therefore, numerous cases are overlooked and misdiagnosed. Even so, it is estimated that 200,000 to 250,000 persons in the United States develop rheumatic fever each year, with 30,000 to 60,000 deaths resulting annually.[4] It is believed that there are more than 460,000 patients with rheumatic heart disease[5] in this country and that this is the most common cause of cardiac death in childhood and young adults.[6] As a result of a survey in New York State, rheumatic heart disease is said to cause more than five times as many deaths as whooping cough, measles, epidemic meningitis and anterior poliomyelitis combined.[7] Although the highest incidence occurs in the decade between five and fifteen years of age, its frequency and seriousness in young adults were emphasized by medical studies in the armed forces during World War II.[1, 2, 8-11]

The prevention of rheumatic fever and rheumatic heart disease is further complicated by the fact that the exact etiology of this condition has not been definitely established.[1] Heredity, nutrition, housing, general standards of hygiene, nonspecific infection, trauma, surgery and many other factors have been implicated.[1, 12, 13] However, it is generally believed that in the vast majority of cases, initial and subsequent episodes of rheumatic fever follow infections of the upper respiratory tract by Group A beta-hemolytic streptococci.[1] Excellent studies have closely correlated the occurrence and absence of cases of rheumatic fever with the incidence of these particular bacteria.[2, 12]

In a recent editorial, Tillett[14] concluded that studies concerning the prevention of rheumatic fever should have decisive priority in any large-scale attack on heart disease. The current literature emphasizes this view. In general there have been two major approaches to prophylaxis in rheumatic fever: prompt and adequate treatment of streptococcal infections in all persons and efforts to prevent the occurrence of such infections in rheumatic persons — those who have had one or more previous episodes of rheumatic fever.[15-17] It has been demonstrated that rheumatic fever subsequently develops in 3 to 6 per cent of cases in streptococcal epidemics; among those who have had rheumatic fever previously the incidence is much higher.[6] Therefore, the American Heart Association Council on Rheumatic Fever and Congenital Heart Disease has recently recommended that adequate therapy be instituted as soon as the diagnosis is reasonably established. Penicillin and aureomycin are recommended in sufficient dosage for ten to fourteen days. It is further advised that the following preparations not be employed: penicillin lozenges, penicillin followed by sulfonamides and sulfonamide drugs.[15-17]

Although early and adequate treatment of streptococcal infections will reduce the occurrence of rheumatic fever with its potentially dangerous sequelae, greatest efforts have been concerned with the actual prevention of these infections in rheumatic patients. Numerous investigations have established that rheumatic fever may be expected to recur in 50 to 70 per cent of cases.[6, 18] These episodes or exacerbations are of progressively increasing severity and tend to be ever more devastating to the heart. An important aspect of the problem of prophylaxis is a realization that perhaps 40 per cent of streptococcal infections are so mild that patients seek no medical treatment, and yet these minimal infections may cause rheumatic fever and rheumatic heart disease.[18]

Since 1939 an extensive literature has evolved concerning the use of sulfonamides in the prophylaxis of rheumatic fever.[19-24] Opinions about the effectiveness of these chemotherapeutic preparations are divergent. Early reports of sulfanilamide therapy

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in children and adults were quite promising. After the development of sulfadiazine, it became the agent of choice in this group of drugs and was most frequently employed. In many short-term studies it was reported that sulfonamide prophylaxis, 0.5 to 1.5 gm. daily being used, resulted in a reduction of respiratory disease by 50 to 75 per cent.[8] This therapy was said to protect 85 per cent of susceptible persons from bacterial respiratory pathogens including hemolytic streptococci.[9] These early studies indicated dangerous constitutional disturbances resulting from the prolonged use of the sulfonamide drugs in only 0.01 per cent and evanescent rashes in only 0.5 per cent.[9]

Subsequent investigations yielded less favorable results. A carefully controlled program disclosed that 1 gm. of sulfadiazine daily was effective initially against Group A beta-hemolytic streptococci but became progressively less so with the appearance of sulfadiazine-resistant strains.[10] These observations were supported by numerous studies in vitro.[25, 26] Some investigators could not demonstrate any beneficial prophylactic effect with sulfadiazine[2, 27]; others believed it to be valuable but emphasized the danger of toxic effects.[28, 25]

Although parenteral injection of penicillin is quite effective in acute suppurative streptococcal infections, its prolonged use would be extremely distasteful and inconvenient. More recently, penicillin given orally has been employed as a prophylactic preparation. Preliminary results are quite encouraging; however, its optimal dosage and method of administration remain to be determined.[11, 15, 29-31] Already, penicillin-resistant strains of Group A beta-hemolytic streptococci are being reported,[32-34] and numerous sensitivity reactions, including several fatal anaphylactoid seizures, have been recorded in the literature.[35] Even now it appears that penicillin will not prevent the recurrence of rheumatic fever in every case.[31]

In 1951 it was decided to investigate the use of aureomycin as a long-term prophylactic agent in rheumatic fever. The effectiveness of this antibiotic against Group A beta-hemolytic streptococci in vitro and in vivo had already been definitely established.[36, 37] In addition, we had been impressed in many cases by the absence of serious toxic effects as complications of long-continued aureomycin therapy.[38-41] No anaphylactoid reactions had been observed. By a reduction of dosage to the range of 1 gm. daily, annoying gastrointestinal symptoms had practically been eliminated.[42] Furthermore, combining the methyl and propyl esters of para-aminobenzoic acid (paraben) with aureomycin had controlled the overgrowth of *Candida* (*Monilia*) *albicans*.[43] In our opinion, the possible danger involved in the long-term administration of a broad-spectrum antibiotic was the development of significant resistance by Group A beta-hemolytic streptococci.

The present paper constitutes a report of the use of aureomycin as a prophylactic agent in 35 rheumatic patients. Comprehensive toxicity studies and bacterial-sensitivity determinations are presented.

Methods

After consideration of blood levels attained with various amounts of aureomycin, it was decided to administer 250 mg. thirty minutes to an hour before breakfast and again two hours after the evening meal. In 4 hospitalized patients subjected to this regimen, blood levels during the twenty-four-hour period ranged from 0.12 to 2.0 microgm. per cubic centimeter; no trace of the antibiotic was detected in 1 case. Subsequently 12 ambulatory patients receiving this medication revealed blood levels ranging from 0.06 to 4 microgm. per cubic centimeter over a period of sixteen hours. In 2 cases no evidence of aureomycin could be demonstrated. It was believed that such levels should be adequate to forestall the majority of infections with Group A beta-hemolytic streptococci in the respiratory tract.[36] Previous clinical observations had indicated that a dosage of this magnitude had few untoward side effects.[42] Aureomycin containing paraben was employed throughout this study.[43]

Placebo capsules* were obtained that were identical in all respects with the aureomycin preparation used in this investigation. The formula for the placebo preparation per capsule was anhydrous dicalcium phosphate, 689 mg., magnesium stearate, 10 mg., mineral oil, 13 mg., and F. D. and C. yellow No. 5 dye, 1 mg. Subsequently the formula was changed to anhydrous dicalcium phosphate, 360 mg., proflo, 360 mg., magnesium stearate, 10 mg., and mineral oil, 10 mg. In this manner a comparable control group could be simultaneously observed for comparative purposes. Neither the patient nor the physician knew which preparation was being given.

Thirty-five patients, all from the lowest social and economic level, were included in this study. Because of the patient's condition and as a result of requests by local physicians, 23 cases were included in the aureomycin group and only 12 in the control series. Eighteen patients receiving the antibiotic had experienced one or more episodes of rheumatic fever in the preceding five years, as compared with 8 among the controls; 5 in the aureomycin-treated and 4 in the control group had had no evidence of activity for more than five years. The average age of the patients receiving aureomycin who had suffered a recent attack of rheumatic fever was seventeen years; among controls it was sixteen years. In the treated group those who had been free of all signs and symptoms of active rheumatic involvement for more than five years averaged forty-nine as compared with thirty-six years for the controls. A total of 32 episodes of rheumatic fever had occurred dur-

*All preparations employed in this study were kindly supplied by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

ing the preceding five years in the 23 patients included in the aureomycin series as compared with 19 such episodes in the 12 control patients (Table 1). There was, therefore, no significant difference between the 2 groups in the frequency of recurrence. A review of the initial onset of rheumatic fever in the aureomycin-treated patients disclosed the following: acute arthritis in 9, early cardiac enlargement in 6, arthralgia in 4, fever and abdominal pain in 4, chorea in 2, subcutaneous nodules in 1, pericarditis in 1, pneumonia and pleuritis in 1. A similar study of the control patients disclosed arthritis in 5, early cardiac enlargement in 3, fever with abdominal pain in 2, arthralgia in 2, chorea in 1, epistaxis in 1, pneumonia and pleuritis in 1. There was no obvious difference in the severity of previous episodes of rheumatic activity in the two groups. Chronic auricular fibrillation was present in 2 patients given the antibiotic and in 1 of the controls. Cardiac decompensation existed in 5 patients in the aureomycin-treated group as contrasted with 3 in the placebo series. One patient receiving the antibiotic had been hospitalized four and a half months previously because of subacute bacterial endocarditis due to *Streptococcus faecalis*. In the aureomycin-treated group 8 patients were males, and 15 were females; among the nontreated patients 7 were males, and 5 were females. In the former group 20 were Negroes, and 3 were white, whereas in the latter, 11 were Negroes, and 1 was white.

Table 1. *Occurrence of Rheumatic Fever in Control and Aureomycin-Treated Patients.*

Series	No. of Cases	Episodes of Rheumatic Fever in 5 Yr. before Prophylactic Study	Episodes of Rheumatic Fever during Prophylactic Study
Aureomycin	23	32 (1.4 per patient)	1 (4.4%)
Control	12	19 (1.6 per patient)	4 (33.3%)

Each patient in this study was examined in the Antibiotic Clinic of the John Gaston Hospital and the University of Tennessee College of Medicine at intervals of approximately six weeks during the fall, winter and spring but only once during the summer season. This reduction in the number of clinic visits was considered justified because of the lower incidence of rheumatic fever in the Memphis area during the summer season. At the time of each examination the following laboratory determinations were obtained: hematocrit, sedimentation rate, white-cell count, urinalysis, nonprotein nitrogen, serum bilirubin, bromsulfalein retention, cephalin-cholesterol flocculation, total and fractional plasma protein and cholesterol and cholesterol esters. Also, an electrocardiogram was obtained every three months.

Results

The period of observation in this study ranged from two to twenty months; the average in the aureomycin-treated group was nine as compared with eleven months in the control series. Thirteen patients were followed for more than one year — through two fall and winter seasons; 7 of these received aureomycin, and 5 placebo medication. The thirteenth remained in the control group for eight months; thereafter, because of four severe respiratory infections characterized by pharyngitis, febrility and constitutional symptoms, she received aureomycin for eleven months. During the latter interval no respiratory infection occurred.

Fourteen patients receiving aureomycin reported fewer respiratory infections than previously, and 9 noted no change, whereas in no case was there an increase in incidence. In the control series 3 noted a reduction, 8 noted no change, and 1 reported an increased number of respiratory infections. Objectively, there was a reduction in excess of 50 per cent in the patients given aureomycin. Of interest was the opinion of each patient regarding his general health: of the aureomycin-treated patients, 17 considered themselves better, 6 noted no change, and not 1 regarded his condition as worse; of the control group, 5 thought themselves better, 6 noted no alteration, and 1 considered himself worse. It is recognized that subjective opinions are notoriously difficult to evaluate. However, the fact that all these patients believed themselves to be receiving the same medication, together with the fact that the examining physician did not know which medication a given patient was receiving, increased the value of these statements.

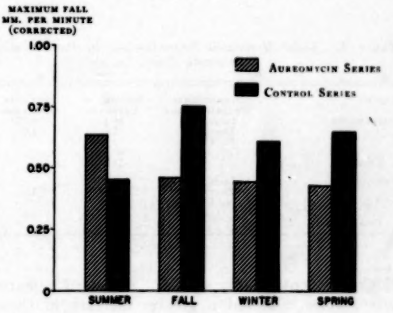

Figure 1. *Serial Sedimentation Rates in Patients with Rheumatic Fever.*

Serial cardiac examinations disclosed a decrease in the size of the heart during this study in 1 patient in each category; however, an increase occurred in 2 patients in the control series. A careful evaluation of cardiac murmurs revealed a decrease in the intensity of a systolic mitral murmur in 1 patient in the control group as compared with 3 in the aureo-

mycin-treated group. A significant reduction in intensity of a Grade 2 mitral diastolic murmur occurred in the patients receiving aureomycin. Of marked interest was the complete disappearance of apical Grade 1 to Grade 2 systolic murmurs in 3 and minimal diastolic murmurs in 2 of the patients given aureomycin; no murmur completely disappeared in the control group. Electrocardiograms disclosed that the QT and PR intervals returned to normal limits in 4 patients receiving aureomycin; however, in another patient, the QT interval became abnormally prolonged (the only relapse in the antibiotic series). In 1 patient in the placebo group (the 1 death in this group) there was evidence of progressive cardiac deterioration (auricular fibrillation developed); no other significant change occurred in the control patients.

Serial determinations of the sedimentation rate (Wintrobe method, corrected) disclosed that the average in the aureomycin-treated patients was consistently within normal limits during the spring, winter and fall seasons but was moderately elevated in the summer (Fig. 1). Aside from the latter period, sedimentation rates in the control group were consistently higher. It should be emphasized that patients were observed much less frequently during the summer. Therefore, the number of determinations was considerably smaller. Repeated hematocrit studies disclosed a greater increase in those receiving aureomycin than in those in the placebo series (Table 2).

TABLE 2. *Serial Hematocrit Determinations in Patients with Rheumatic Fever.*

SERIES	HEMATOCRIT DETERMINATION	NUMBER OF PATIENTS	AVERAGE INCREASE
Aureomycin	Increased	16	cc.%
	Decreased	5	2.3
	No Change	2	
Total		23	
Control	Increased	9	
	Decreased	3	1.4
	No Change	0	
Total		12	

Five recurrences of rheumatic fever occurred during the course of this study (Table 1). Four were in the control group and only 1 was in the aureomycin series. The 1 recurrence among the patients receiving the antibiotic must be regarded as a definite failure of prophylaxis. This patient was a thirteen-year-old Negro girl whose initial attack of rheumatic fever had occurred a year previously. For eight months while receiving aureomycin she had suffered no respiratory infection, and six successive examinations in the Out-Patient Department had been nonrevealing. However, on March 19, 1952, acute arthritis and profuse epistaxis developed. After admission to the hospital and routine therapy, this patient was again placed on aureomycin and has remained in excellent health. Two patients died during this investigation, 1 in each group. However, whereas autopsy in the control case established the existence of active rheumatic heart disease, with death resulting from embolism, death in the patient receiving the antibiotic was not related to the rheumatic state. It should be noted that 2 patients included in this report were subjected to mitral commissurotomy. Both received aureomycin prophylactically before and after surgery. No complication developed in either case.

Toxicity

Side effects of aureomycin prophylaxis observed during this investigation are presented in Table 3. In only 1 case was it necessary to discontinue medication because of toxicity. This occurred in a thirty-year-old white woman with a previous diagnosis of psychoneurosis made by psychiatric consultants. Although this patient complained of severe pruritus vulvae following three months of aureomycin treatment, examination was entirely negative, and laboratory studies disclosed no yeast or other pathogenic organisms. This woman had had similar symptoms with penicillin by mouth that had necessitated its discontinuance. She was also unable to tolerate sulfonamides. No follow-up study was possible in this case since the patient moved from the Memphis area. Of extreme interest was the observation that a definite increase in appetite occurred in 7 persons receiving aureomycin. Two of those in the control group likewise noted an improvement in appetite but only after supplementary vitamins had been administered. Bacteriologic examination of the stool in the 1 patient with diarrhea (4 stools per day for four days) disclosed *Escherichia coli* and *Str. faecalis*. Neither *C. albicans* nor hemolytic strains of *Staphylococcus aureus* were demonstrated. Although comprehensive liver-function tests were performed regularly in all cases, no evidence of hepatic toxicity was observed. A bone-marrow examination, which was carried out in 1 case in each group because of transient, borderline leukopenia (white-cell counts of 3700 to 4400), revealed no abnormality in either, and shortly thereafter, peripheral blood findings became persistently normal.

TABLE 3. *Side Effects of Aureomycin Prophylaxis.*

SIDE EFFECT	NO. OF CASES
Nausea (mild, transient)	4
Vomiting (total of 4 episodes)	2
Diarrhea (4 stools daily for 4 days)	1
Constipation	1
Increased flatulence	2
Pruritus ani (duration of 2 days)	1
Pruritus vulvae	1

Bacterial-Sensitivity Studies

In an attempt to demonstrate the possible development of resistance by Group A beta-hemolytic streptococci to prolonged aureomycin therapy, pharyngeal and tonsillar specimens (sterile cotton swabs being used) were obtained initially and thereafter at approximately six-week intervals in 450 cases. In addition to the 35 patients included in the rheumatic study, more than 400 geriatric patients, half of whom were receiving similar prophylactic therapy for other conditions, were given this examination. The geriatric cases were observed for longer periods than those in the rheumatic series. The average observation in the former group ranged from fifteen to twenty-one months. This study on bacterial resistance will be reported in a separate paper.

All throat swabs were inoculated within one hour on 5 per cent human blood-agar plates. Grouping of beta-hemolytic streptococci was carried out by

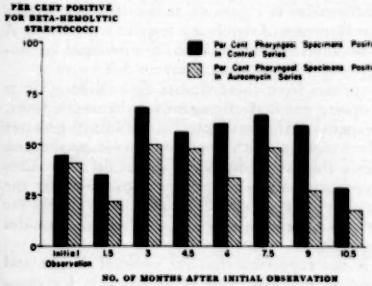

FIGURE 2. *Effect of Aureomycin on Incidence of Beta-Hemolytic Streptococci.*

the capillary precipitin method of Swift, Wilson and Lancefield.[44] The tube dilution method was employed to determine the sensitivity of Group A beta-hemolytic streptococci to aureomycin, the tube-to-plate technic being utilized to determine the results.[26, 45] The bacteriostatic rather than the bactericidal concentration was reported as the end point. The bacteriostatic point was defined as the minimal concentration of aureomycin that yielded only a small number of isolated colonies on blood-agar plates.

Group A beta-hemolytic streptococci were frequently not completely eradicated by 500 mg. of aureomycin daily (Fig. 2). They were, however, persistently and significantly reduced. It was possible to investigate adequately alterations in the sensitivity of Group A beta-hemolytic streptococci to long-continued aureomycin treatment in 44 patients who repeatedly harbored these organisms. Twenty-four of these persons were from the control group, and 20 were in the aureomycin series. The

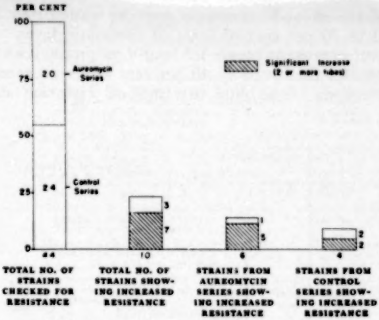

FIGURE 3. *Increased Resistance of Beta-Hemolytic Streptococci to Aureomycin.*

results of these sensitivity determinations are presented in Figures 3, 4 and 5. It appears that the long-term administration of 500 mg. of aureomycin

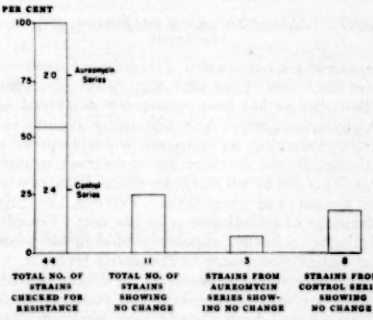

FIGURE 4. *No Change in Resistance of Beta-Hemolytic Streptococci to Aureomycin.*

daily does not result in the development of significant resistance by Group A beta-hemolytic streptococci.

DISCUSSION

By far the leading cause of death today is cardiovascular disease. It was recently emphasized that in any large-scale attack on cardiac disease, primary attention should be given to the prevention of rheumatic fever.[14] Prompt diagnosis and adequate treatment of streptococcal infection involving the respiratory tract greatly reduce the incidence of rheumatic fever and rheumatic heart disease. For this purpose penicillin or aureomycin has been recommended.[15-17]

However, the actual prevention of such infections in rheumatic patients provides the best prospect of effectively controlling the rheumatic state. Such persons are relatively susceptible to streptococcal infections, and recurrence may be anticipated in 50 to 70 per cent of cases of rheumatic fever. A most important reason for long-term prophylaxis is the fact that possibly 40 per cent of streptococcal infections are so mild that medical attention and

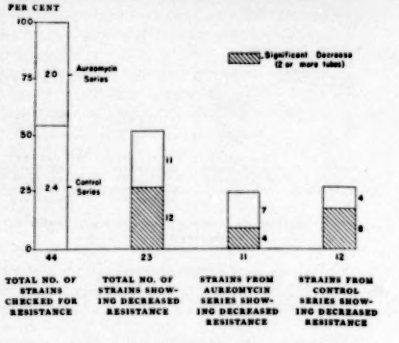

FIGURE 5. *Decreased Resistance of Beta-Hemolytic Streptococci to Aureomycin.*

treatment are not sought. Nevertheless, rheumatic fever may result from such minimal involvement.[15]

Sulfadiazine has been extensively employed as a prophylactic agent. Although many reports have been encouraging, its prolonged and widespread use is limited by the development of resistant strains of organisms and by various toxic effects, some of which are serious and even fatal. Perhaps the prime advantage of sulfadiazine is its low cost. Penicillin, administered orally, appears promising for protection against recurrence of rheumatic fever; it, too, is not excessively expensive. However, penicillin studies are still preliminary, and resistant strains of streptococci have already been reported. Also, toxic effects, including a few that have been fatal, are occasionally recorded in the literature.

In the present study only 1 recurrence occurred in 23 rheumatic patients receiving 500 mg. of aureomycin daily for an average of nine months. This constituted a recurrence rate of 4.4 per cent. The duration of therapy ranged from two to twenty months, 6 patients being observed for a year or more. Four recurrences developed in the control series of 12 persons who were followed for an average of eleven months. This was a recurrence rate of 33 per cent. In an additional case in the control series 4 severe respiratory infections developed during a period of eight months, and the patient was therefore transferred to the aureomycin series. During the ensuing eleven and a half months no respiratory infection occurred.

A reduction in respiratory infections of approximately 50 per cent was observed in patients receiving aureomycin. In addition, subjective and objective evidence indicated definite improvement in health in the aureomycin-treated as compared to the control patients. The administration of placebo medication, together with the method of treatment employed, kept both the patient and the physician from being aware of the type of medication being administered.

One death occurred in each group of patients. Autopsy in the case from the control series revealed active rheumatic heart disease; the death in the aureomycin-treated group was unrelated to rheumatic fever.

Therapeutic side effects were minimal. It was decided to discontinue aureomycin in only 1 case, although the development of significant toxicity was doubtful. Gastrointestinal symptoms were minimal, and laboratory procedures failed to demonstrate any overgrowth of either *C. albicans* or hemolytic *Staph. aureus* as a result of prolonged aureomycin treatment. Extensive sensitivity studies involving approximately 450 persons failed to demonstrate the development of significant resistance by Group A beta-hemolytic streptococci to the prolonged administration of 500 mg. of aureomycin daily.

It appears from these studies that aureomycin is a promising prophylactic agent for rheumatic fever. The expense of this antibiotic constitutes its greatest disadvantage but with improvements in production methods this problem should be minimized. Certainly, a great sense of security is provided by the realization that an effective agent is available for those who are unable to tolerate either sulfonamides or penicillin.

It is not suggested that the optimal dosage and method of administration of aureomycin for rheumatic prophylaxis has been established. Additional investigation is essential.

SUMMARY AND CONCLUSIONS

Aureomycin appears to be an effective prophylactic agent in rheumatic fever. This antibiotic may be less dangerous for prolonged use than either sulfadiazine or penicillin. Extensive studies revealed no evidence of the development of significant resistance by Group A beta-hemolytic streptococci to prolonged aureomycin therapy. This antibiotic should be of great value in cases in which patients are unable to tolerate either sulfonamides or penicillin.

We are indebted to Mr. Robert R. Threlkeld for his assistance in the bacterial-sensitivity studies and to Miss Larey Evans, Mrs. Regina Benson and Miss Mary Jean Watson for their technical assistance.

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OCCURRENCE OF THYROID CANCER*

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FOR many years there has been disagreement over the incidence of carcinoma of the thyroid gland. Some authorities have claimed that it is a relatively common disease, and others have maintained that it is extremely rare. Such differences of opinion about a basic fact have led to irreconcilable differences in matters of judgment. Much of the controversy over the management of nodular goiter, for example, stems from conflicting opinions about the incidence of thyroid cancer. This has been a subject of discussion since the beginning of this century. Müller and Speese,[1] in one of the first reviews of thyroid cancer in the American medical literature, indicated that it was a rare disease. Wilson,[2] on the other hand, argued a few years later that it was much more frequent than had been assumed and deplored the paucity of papers on this subject in American journals. The situation in recent years was well summed up in an editorial,[3] as follows:

> Much of the recent literature concerning the thyroid gland has emphasized the conflicting opinions that exist regarding the incidence of carcinoma of this structure, and the interpretation of the nodule in the gland as precancerous. On the one hand reports from surgical clinics where an aggressive attitude is followed disclose that carcinoma is discovered in a large percentage of apparently innocent nodules; opposed to this are the analyses of routine autopsy material indicating a very low incidence of thyroid carcinoma as a cause of death. . . . Currently, evidence of cancer is found in about 20 per cent

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of the single nontoxic nodules that are removed surgically at the Massachusetts General Hospital. This high incidence of thyroid cancer may be contrasted with the experience at the Pondville Hospital, where only 46 cases have been encountered in twenty years, or approximately 1 case among every 300 cases of all types of cancer. . . .

Such disagreement over the incidence of a disease is quite unusual in modern medicine, and an attempt to resolve it appears worth while. Sufficient information has been accumulated during the past three decades to answer the question, "How common is thyroid cancer?" It is widely scattered, however, and much of it is in sources not usually read by clinicians. Such material has been collected and, with some data from the Tumor Registry and the Department of Pathology of the Yale University School of Medicine, is reviewed in this paper. The following types of statistics will be discussed: clinical data, from tumor registries, armed forces morbidity reports and cancer surveys; mortality statistics, from official mortality tables and other sources; and autopsy statistics, from several medical centers.

Another source of information on this subject consists of reports based on surgical experience with patients with thyroid disease coming to operation. Such statistics have been collected, but since they require somewhat lengthy analysis and cannot be compared directly with the types of information listed above, they will be evaluated separately in another paper.

Clinical Data

Table 1 lists the frequency of cancer of the thyroid gland as reported by various observers. On the average, it represents 0.56 per cent of clinical cancer. It is seen that there is good agreement among the various sources cited, with none varying more than 40 per cent from the average. There is some duplication between the figures for Connecticut and for the Yale Tumor Registry; this does not affect the final average appreciably. The figure from the Pondville Hospital may perhaps be too low, owing to "competition" from the famous thyroid clinics in the Boston area. This is balanced by the figure from the Yale Tumor Registry, which is somewhat high. For a time this was the only medical center in Connecticut using radioactive iodine, and a significant number of patients with thyroid tumors were referred here from distant clinics. Thus, the figure from this institution is higher than that for the entire state, as reported by the State Department of Health.

The study by Dorn[8] merits particular attention. It is one of the most thorough investigations of cancer incidence and prevalence ever carried out. A painstaking survey was made in 10 metropolitan areas of the United States, containing 10 per cent of the country's total and 18 per cent of its urban population. Every hospital and 98 per cent of the practicing physicians in these areas co-operated in identifying patients under treatment or observation for cancer. The more goitrous population of this country is heavily represented in this survey, since Chicago and Detroit constituted 2 of the areas.

Table 1 combines incidence and prevalence data. (Prevalence refers to the total number of cases in a population, whereas incidence refers to the number of new cases arising during a certain time interval.) It was not feasible to separate these somewhat different expressions of clinical frequency. Since thyroid cancer runs a somewhat longer course, on the average, than most cancers, its relative prevalence may be a little higher, and its relative incidence a little lower, than the average shown for the combined data.

Table 1. *Clinical Frequency of Thyroid Cancer.*

Source of Data	Population	Period of Study	All Cancers*	Thyroid Cancer	
				Cases	Percentage of All Cancer
Harnett[4]	Greater London	1938–39	14,000	99	0.70
Lindsey & Cohart[5]	U. S. Army	1944	3,000	24‡	0.8
Editorial[3]	Pondville Hospital,† Massachusetts	(20 yr. before 1947)	13,000‡	46	0.33
Dorn[8]	Urban White, U. S.	1937–39	40,000	257‡	0.65
McSwain and Williams[7]	Vanderbilt Univ. Hosp., Nashville, Tenn.	1925–48	4,000	30	0.8
Connecticut State Department of Health	Connecticut	1935–46	38,000	159	0.42
Sokal	Yale Tumor Registry	1923–52	10,000	65	0.65
Aggregate			122,000	680	0.56

*Approximate figures.
†State cancer hospital.
‡Not explicitly stated but calculated from data.

Mortality Statistics

Mortality statistics, in general, show a somewhat lower incidence of thyroid cancer than the corresponding clinical data. Table 2 presents some figures that may be compared with those cited above. On the average, thyroid cancer accounted for 0.41 per cent of cancer deaths. There is remarkably little variation among the large populations from so-called "nongoitrous" areas. The figure from the Yale Tumor Registry, which is the highest in the table, does not represent a true sample of Connecti-

cut, as indicated above. The higher figures from Switzerland lend support to the postulate that goiter is a premalignant lesion.

Autopsy Material

Table 3 shows the incidence of cancer of the thyroid gland in several series of autopsies. The average was 1 case per 1200 deaths. The difference between the figure from the Boston City Hospital and this average was not statistically significant — that is, the probability that it was a chance variation is greater than 0.05. In several cases the thyroid cancer was an incidental finding and not a cause of death.

The validity of such autopsy data has been denied by a number of authors,[15, 16, 17] who claim that on conclusions drawn from autopsy figures is typical of this point of view:

> We believe that this is fallacious reasoning and that the apparent discrepancy is due to the fact that in fatal cases of thyroid cancer the patient has usually had the disease for a long time before the terminal stage is reached and that, except for an occasional patient who is rushed into the hospital in acute dyspnea and for the rare operative mortality, these patients usually die at home.
>
> ... The significant fact we believe to be this: in a period shorter by two years than that covered by the autopsy survey we found 11 patients ... who are known to be dead of thyroid cancer. Only 1 of these came to autopsy, and that one at another hospital. ...

The authors who used the argument quoted above seem not to have realized that any autopsy series represents only a small sampling of deaths. Not only most patients with thyroid cancer but also the great majority of all patients are not autopsied. Even in communities with large university hospitals, no more than 10 to 15 per cent of patients are studied at autopsy. The pertinent question is, How does the autopsy percentage in a particular disease compare with that for all disease, or for some disease group that may serve as a reference? In general, illnesses in which there is considerable interest and thyroid cancer is much more frequent than is indicated in Table 3 but that the great majority of its victims do not reach autopsy. As evidence, individual experiences were cited in which patients known to have died of thyroid cancer failed to come to autopsy. The largest of such illustrative series consisted of 11 patients. The following comment[15]

Table 2. *Frequency of Thyroid Cancer as a Cause of Death.*

Source of Data	Population	Period of Study	All Cancers*	Thyroid Cancer	
				cases	percentage of all cancer
Relatively "nongoitrous" populations:					
Harnett[4]	Greater London	5-yr. follow-up of 1938–39 cancers	11,000	55	0.50
U. S. Vital Statistics	Total United States	1939	154,000	621	0.40
U. S. Vital Statistics	Total United States	1949	206,000	814	0.40
Sokal	Yale Tumor Registry	1923–52	7,000	42	0.6
Totals			378,000	1532	0.405
Harnett	England and Wales Registrar-General's statistics	1938–39	—	—	0.41
Bertelsen et al.[6]	Denmark	Before 1947	—	—	0.4
Cohart[7]	U. S. Army	1944	—	—	0.5
Severely goitrous populations:					
Wegelin[10]	Switzerland	1901–10	—	—	1.6
Wegelin	Switzerland	1911–20	—	—	0.98

*Approximate figures.

Table 3. *Frequency of Thyroid Cancer among Autopsies.*

Source of Data	Institution	Autopsies*	Thyroid Cancer	
			total cases	as cause of death
Staemmler[11]	Charity Hosp., Berlin, before 1914	13,000	13	Not stated
VanderLaan[12]	Boston City Hosp., Boston, 1896–1945	18,700	5	4
VanderLaan[12]	Massachusetts Gen. Hosp., Boston	11,000	10 or less	Not stated
VanderLaan[12]	Peter Bent Brigham Hosp., Boston	6,000	5	Not stated
Anglem and Bradford[13]	Massachusetts Memorial Hosp., Boston, 1934–47	1,700	0	—
Sokal	New Haven Hosp., New Haven, 1917–52	9,700	12	10
Jaffé [14]	Cook County Hosp., Chicago	1,000	2	2
Ophüls[15]	Dept. of Pathology, Stanford Univ. Med. School, San Francisco, 1900–23	3,000	1	Not stated
Dailey et al.[16]	Univ. of California Hosp., San Francisco	1,700	4	Not stated
Dailey et al.[16]	Los Angeles County Hosp., Los Angeles	36,500	34	Not stated
Aggregate		102,300	86†	16 out of 19

*Approximate figures.

†Incidence of thyroid cancer found among autopsies, 0.084 per cent.

active investigation, as well as most rare diseases, tend to be studied at autopsy somewhat more frequently, whereas such causes of death as cerebrovascular accidents appear less frequently than they should.[18]

One would expect, therefore, that carcinoma of the thyroid gland would come to autopsy more frequently than most diseases. And, in fact, the available data indicate that this may be so. Table 4 gives some suggestive figures on this point.

TABLE 4. *Autopsies in Thyroid Cancer and in Other Diseases.*

CATEGORY OF DISEASE	DEATHS*	PERCENTAGE AUTOPSIED
New Haven, Connecticut:		
All deaths, New Haven County, 1950	5,300	12
Yale Tumor Registry, cancer of lung, 1950–52	120	23
Yale Tumor Registry, cancer of breast, 1923–50	590	9
Yale Tumor Registry, thyroid cancer, 1923–52	42	48
London, England — 5-yr. follow-up of 14,000 cancer patients registered in 1938–39:		
All cancer	11,000	24
Cancer of lung	1,000	43
Cancer of breast	1,400	10
Thyroid cancer	55	31
University of California, San Francisco:		
Cancer of breast, 1918–47[19]	750	9
Thyroid cancer, 1935–47[19]	23	At least 17†

*Approximate figures.
†Data given in reference insufficient for calculation of actual percentage.

DISCUSSION

The findings of this review are summarized in Table 5, which gives the frequency of thyroid cancer for each of the three categories of statistics surveyed. The autopsy data have been recalculated to express thyroid cancer as a percentage of all cancer, instead of as a percentage of all deaths. This standard of reference has been used because it is convenient and relatively stable. The position of cancer as a cause of morbidity and mortality has changed considerably during the past fifty years and is still changing. However, the ratio of individual cancers to all cancer has changed little, with a few exceptions. Such a ratio can be used to compare statistics from different years (and to some extent, for diverse population groups), whereas crude incidence and mortality rates cannot. Conversion of the autopsy figures into the desired form was readily accomplished. The incidence of cancer in several large autopsy series (including two fifths of the autopsies in Table 3) averages a little over 17 per cent,[18, 20, 21] and there is very little variation among large general hospitals in this respect. The values listed were obtained by application of this factor to the figures in Table 3.

TABLE 5. *Frequency of Thyroid Cancer, as a Percentage of All Cancer.*

SOURCE OF DATA	CLINICAL FREQUENCY		CAUSE OF DEATH	
	RANGE %	AVERAGE %	RANGE %	AVERAGE %
Table 1 (clinical data)	0.3–0.8	0.56		
Table 2 (mortality statistics)			0.4–0.6	0.41
Table 3 and text (autopsy statistics)			0–1.3	0.47
Aggregate		0.56		0.44

As indicated above, the autopsy figures might give somewhat too high an incidence of thyroid cancer as a cause of death. On the other hand, mortality tables might show too low an incidence, since it is more likely that patients will die of an undiagnosed thyroid cancer than that death will erroneously be attributed to this cause. However, there is actually little difference between the two figures. This suggests that the error in each type of statistics is less than has often been assumed.

The clinical frequency of thyroid cancer is seen to be somewhat higher than its frequency as a cause of death. This is consistent with current experience that cancer of the thyroid gland is more "curable," on the average, than most cancers.

The experience summarized in Table 5 extends over half a century in time and from Berlin to Los Angeles in space. The agreement among different types of statistics from various sources is remarkably close. It is difficult to see how such uniformity could have been achieved by chance or through the operation of a systematic error. It must be concluded that these figures are valid.

It is instructive to express the conclusions of this study in terms of what might be expected in a "typical" community. A hypothetical city with a population of 1,000,000 makes a convenient example. In such a city, there would be 25 patients with thyroid cancer, 1 new case would appear every month, and there would be 6 deaths per year from thyroid cancer, 1 or 2 of which would be studied at autopsy.

Certain surgical statistics appear to be in conflict with the figures presented in this paper. Various authors have reported that a high percentage of nontoxic nodular goiters are found to be malignant at operation. Since such goiters are known to be quite common, many physicians have concluded that thyroid cancer must be more frequent than has been indicated here. This discrepancy is more apparent than real, and is explained by the fact that nontoxic goiters reaching the operating table are a highly selected group and are not at all representative of such goiters in the population at large. This point was emphasized by Crile and Dempsey,[22] but does not yet appear to be generally appreciated. A detailed analysis of surgical statistics on thyroid cancer will be published separately, but it is appropriate to state here that it indicates that fewer than 1 per cent of unselected nodular goiters are malignant.

Summary and Conclusions

The frequency of thyroid cancer can be given with considerable accuracy. This disease represents slightly more than 0.5 per cent of clinical cancer and accounts for slightly less than 0.5 per cent of deaths from cancer.

In a typical community of 1,000,000 there would be 25 patients with thyroid cancer. One new case would appear monthly. There would be 6 deaths per year from thyroid cancer, and 1 or 2 of these cases would be studied at autopsy.

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PUTTING THE FAMILY BACK IN MEDICAL EDUCATION*

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PHILADELPHIA

SIGERIST has described the function of medicine as follows:

> The task of medicine is to promote health, to prevent disease, to treat the sick when prevention has broken down and to rehabilitate people after they have been cured. These are highly social functions and we must look at medicine as basically a social science — one link in a chain of social welfare institutions that every civilized country must develop. If we have a maladjustment today, it is to a large extent due to the fact that we have neglected the sociology of medicine. The *technology of medicine has outrun its sociology*.... In the civilized society of tomorrow the physician will become a public servant — and medicine will increasingly shift the emphasis from disease to health.

Sigerist puts in terse form his concept of the historical perspective in which society is living medically — a turning point in medical education and practice. Medical technology has outrun not only its sociology but also its psychology. The importance of social, environmental and emotional factors in the development of much medical illness and their consideration in effective treatment are frequently overlooked, owing to the many changes in the practice of medicine in the last generation. There has been a shift from home to hospital and clinic practice, laboratory medicine has increased, and the compartmentalization of medical knowledge and skill has given rise to specialists and physicians in group practice, who are replacing general practitioners. With all its gains this has had its evils; values of effective practice have been lost. For it has been the family doctor who has considered the needs of the patient himself as a person in his own individual setting.

A survey was recently made of community attitudes toward physicians, of what people expected from them and how well they thought their needs were being met. A general feeling was expressed that doctors were usually too busy to listen and talk with their patients or to try to understand the emotional factors growing out of family, economic or sociologic stresses. All through these reports it was thought that the human side of medical practice had been increasingly sacrificed, that mechanism was crowding out spirit, the patient often being lost in the nexus of speed, organization, many appointments, business, measurement, organs and reports. In the complexity of ultrainvestigativeness, the personality, the individuality, the feelings, the patient himself, for whom all this exists, disappears. Ultrascientific aloofness and detachment, called objectivity, often appear to the patient as indifference, complacency or even rejection, as if his visit to the doctor were an unwelcome intrusion in a busy professional schedule.

Sometimes, even in psychiatry, the mind or soul has been lost in the impersonality of mechanisms and processes. Values and integrations are replaced

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by formulas and reactions. A young wife in early marriage became depressed. She had been an only child, with many illnesses in childhood. She had been overprotected. She was not prepared for marriage. The doctor was so intrigued with the intellectual puzzle of her personality — he was so engrossed with the mechanisms of her problem — that he gave no evidence of warmth and caring. His scientific curiosity outran the call of urgency and practicality. The patient remarked that her fancy doctor did not care whether she lived or died. It seemed to be no concern of his. Her old Negro mammy helped more than the experienced physician by patting her on the shoulder as she passed her at the dining-room table, saying, "Dat's all right, missy, you just keep trying and this will go."

Then there was the case of the young resident scared to death — in a panic — an anxiety state. The doctor who treated him sat there mute as a sphinx, trying to force him to shell off the layers of his personality so that he could understand the mechanisms of his disorder. The patient did not experience the warmth, interest and caring that were necessary for carrying him through this stage of his illness. His therapist was searching for the mechanisms of his reactions. There was no humanness. The patient said that psychiatry was purely mechanistic and uncaring, with no warmth, religion or idealism.

A middle-aged mother had a hysterectomy because of a disturbance in menstruation. Too great reliance was placed on the surgeon's examination and palpation, which was in error. There was an insufficient exploration of her emotional and erotic frustrations, which were threatening to destroy her family and herself. The hysterectomy was more dramatic than psychiatry and temporarily definitive, and at least was doing something to the patient. A uterine suspension did not relieve a pain in the back, since this was really a substitute for a pain in the neck or resentment at the husband's limitations and inconsiderateness.

The psychiatrist sees numerous examples of the lack of comprehensive medicine — the lack of appreciation of the patient as a person and of feeling factors in disturbed physiology and in organic disease. He sees lack of recognition of the importance of family background, family attitudes, directions, limitations, prejudices, intolerances, threats, anxieties and irritations in relation to disease. These are factors that the old general practitioner or family doctor recognized because he was familiar with the family setting in which the illness appeared. Much of his practice can be comprehended under the term the art of medicine. Science has its limitations in the practice of medicine. There is a significant percentage of general practice in which there are disabling discomforts and suffering, for which physical findings and abnormal measurements are absent. Art is the ability to go beyond demonstrable fact and the scientific recommendations of therapy; it is the ability to apply experience, to use judgment and tact, to communicate with others — the patient and his family — to be tolerant, sympathetic and understanding, to diminish anxieties, and to reduce resentments and help people meet and bear frustrations. Art here is cultivation of strength and resources; it is a growing, constructive relation. There is something in the art of therapy that is like the artistic experience — expanding, life-giving, strengthening and inspiring. Science cannot always give that. The family doctor long ago learned the healing value of personal relations and helping attitudes. He knew how to look beyond the disease to the patient, and from the patient to the family, and behind the family to his cultural and religious background.

Apprenticeship teaching enables the young physician to absorb some of these insights and tools of therapy. This type of teaching had values that were lost in large measure by the great advances of laboratory medicine, the application of physics and chemistry to the understanding of disease and its treatment. This progress is certainly not to be decried, because of the great gains individually and socially in the diminution of suffering and deaths. But one of the goals of present-day medicine is the reintegration of the patient, his feelings, personality and background into teaching and practice. The lack of recognition of these aspects has led to untold suffering, useless surgery, the prolongation of convalescence, the cultivation of chronicity, the facilitation of neurosis and the encouragement of irregular practitioners and quacks.

The Family Health Advisor Service and the new Division of Family Study (which operates a marriage-counseling service) at the University of Pennsylvania School of Medicine tend to counteract the neglects and deficiencies indicated above in the practice of medicine and in medical teaching, including again the values of the general practitioner and the family doctor. They re-emphasize the significance and value of the family in medical education.

In the Family Advisor Service the student is assigned a family by the Social Service Department, making contact with the family usually through one of its members who has been a patient in the hospital or an outpatient. For four years he acts as a friendly adviser for the family, keeping track of events, whether medical, economic or sociologic — the growth and development of its members and the effect of illness, injury or emotional conflict. He visits the family once a month if there is no illness and more frequently if there is illness or trouble. He observes the sanitary level of the home and neighborhood, the presence or absence of recreational opportunities, the interaction of various members of the family, the presence or absence of emotional tensions and conflict and their influence on the

various members of the family. In emergencies the student can call on a faculty adviser. A small group of students meets once a month for discussion with a faculty group consisting of an internist, pediatrician or surgeon, a social worker and a psychiatrist. The home and the family thus become the first laboratory for the study of human relations. The student learns the importance and meaning of persons in the home, their influence on illness and the effect of illness on the family. He learns the difficulties of establishing satisfactory relations between doctor and patient and the importance of good relations. He learns to see how his own characteristics — his prejudices, anxieties, expectations and irritations — may influence these relations destructively. He learns the pitfalls of overidentification and overdependence.

The Family Health Advisor Service facilitates learning through personal contact with medical and family problems from the first year of medical school. It encourages maturation through gradual assumption of responsibility. The student does not prescribe medical treatment. It is not a home-care program. The student acts as an adviser or coordinator or interpreter of the hospital and doctors to the patient, and family, or of the patient and his family to the hospital and its doctors or to the family physician. Every sort of problem comes up in connection with the health of the individual members of the family — such as the treatment of a pregnant mother who had syphilis or diagnosis of measles and discovery of community resources for supplying preventive inoculations of globulin to a younger sister. Students were asked their opinion on the advisability of an operation and how to cure a child of enuresis. A man of eighty-two was helped to meet the anxieties of old age. An overburdened mother of 5 children, trying to carry on her housework, was helped by her student adviser to have a valvulotomy, which restored her ability to carry on successfully without cardiac difficulties. Another student, impressed by the lack of recreational facilities for the children in his family, was instrumental in the establishment of a playground in a churchyard in a crowded slum section of the city. Owing to the interest, zeal and discussion of one of the students a family in a low-income bracket tripled its income and was able to move from a poor housing area, thus greatly improving its economic and social position.

The course supplies practical, vivid motivation for learning. It gives the perspective the family doctor has always had; the importance of family, home, economics and sociology is taken in, not through lectures but in actual experience. The student develops confidence in his ability to make contact with people. He learns to deal with his own limitations and dispense with the façade of omniscience. He can say, "I do not know," with self-respect. He learns the importance of feelings and personal and family relations, as well as basic science, in the practice of medicine. This experience militates against the impersonality and depersonalization of the customary first two years of the study of medicine. It provides the humanitarian interest of service, which is an important motivation for many who enter medicine. The student learns the healing value of human interest, discussion and help that comes through working with people and participating in the search for the solution of problems. He learns, in the words of Cherkasky, "that to understand what caused this patient to become sick, it is necessary to know about the patient's family, where he lives, what kind of clothes he wears, what food he eats, what kind of employment he has, and how he reacts to these factors":

> These and similar factors make up man as a social being and may be more provocative in the origin of disease than the germ which has been isolated from the sputum in the bacteriological laboratory. The hospital must seek a knowledge of these factors as eagerly as it seeks knowledge in the field of scientific medicine.

There is not time to report on the work of the new Division of Family Study. This will be done elsewhere. Through this division senior medical students are offered sixteen lectures on family attitudes and sexual behavior. A few selected seniors also are enabled to work in a marriage-counseling clinic, where they learn at first hand the effect of family attitudes and behavior in promoting well being or maladjustment or illness.

The paradigms of Virchow, Koch and Pasteur are no longer adequate for an understanding of disease, monumental and revolutionary though their contributions were. The same reservation may be made of the application of formulas and concepts of physics and chemistry, however comprehensive and desirable they are. But fear, insecurity, resentment, environmental changes and family stresses, as well as bacteria, noxious agents, trauma and tumor, can change chemistry and physiology. Emotions as an important cause of disturbed physiology, chemistry or homeostasis, stressful experience as a source of disease and the importance of environmental conditions, especially family conditioning as predisposing to emotional and psychosomatic illness, — concepts that were introduced by Cannon, Selye, Pavlov and Freud, — must be brought into the practice of medicine. Only then can one speak of comprehensive medicine.

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MEDICAL PROGRESS

VIRAL HEPATITIS*

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A NUMBER of new developments have occurred in the field of viral hepatitis since the last review of this subject in 1948.[1] The purpose of the present report is to summarize the studies on infectious hepatitis and homologous serum hepatitis published since that time.

Although attempts at transmitting hepatitis virus to laboratory animals continue to be uniformly unsuccessful, Colbert[2] believes that on the basis of experimental disease produced in human volunteers, the virus of infectious hepatitis may be differentiated from that of serum hepatitis although they apparently belong to the same general group. Infectious hepatitis (IH) virus has an incubation period of ten to forty days, with an average of twenty-five days. The virus is transmitted through the ingestion of infected material and can be demonstrated in the feces and blood of patients in the active phase of the disease. The virus is not demonstrable in the blood halfway through the incubation period or in the stools or serum twenty-six days after the onset of disease although it has been demonstrated in the blood three days after the onset of symptoms. Recently, evidence has been presented that a fecal carrier state lasting four months to a year after the onset of infectious hepatitis can exist and that the virus obtained from such patients can cause acute disease in volunteers. Serum hepatitis (or SH) virus has an incubation period of sixty to a hundred and fifty days or more. The virus can be recovered only from blood and blood products and can be demonstrated in the blood during both the long incubation period and the acute phase of the illness. The agent was absent late in the disease in one experiment. Because of these differences, infectious hepatitis and homologous serum hepatitis continue to be considered separately for the purposes of review.

INFECTIOUS HEPATITIS

Viral Studies

One of the most important developments in this field has been the successful passage of the virus of infectious hepatitis through tissue culture and the embryonated hen's egg by Henle and his co-workers.[3] The viral agents were obtained from serum or stool suspensions of patients during the acute stage of two outbreaks of infectious hepatitis involving the Akiba and NL strains. The agents were passaged in tissue cultures of rabbit liver cells in roller tubes and minced chick embryos in Simms-Sanders medium followed by passage into the amniotic cavity of the chick. The cultures of both strains induced mild hepatitis without jaundice in the majority of volunteers tested, after an incubation period ranging from nine to thirty-eight days. In his study of the disease produced by the passaged material, Drake[4] compares the disease caused in volunteers by cultivated viruses and that produced by natural infectious hepatitis virus. Both types of viral preparations caused illnesses in a comparable number of volunteers (83 per cent in passaged and 75 per cent in natural) after similar average incubation periods (twenty-four-and-four-tenths days in passaged and twenty-three-and-four-tenths days in natural). The average duration of disease was the same for both types of virus — twenty-eight days. The disease could be divided in both groups of patients into a primary stage, followed after a short interval of relative well being by the secondary stage. The illnesses in both were characterized by anorexia, nausea, vomiting, enlarged, tender livers and abnormal liver-function tests, with frequent temperature elevations. They differed in that jaundice was observed in 31 per cent of the cases resulting from infection with natural virus but in none of the patients infected with the cultivated virus. Those convalescent from infection with the cultivated virus were found to be immune when exposed to natural infectious hepatitis virus.

Stokes and his associates[5-7] have irradiated with ultraviolet light amniotic fluid harvested from the fifth and later egg passages of the Akiba strain, and have used the material as a skin-test antigen for infectious hepatitis; 0.1 cc. of the amniotic fluid was injected intracutaneously in one arm and an equal amount of nonirradiated, uninfected amniotic fluid was injected in the other arm as a control. The positive tests showed both redness and induration, varying usually from 10 x 10 mm. up to 50 x 50 mm. The test was considered negative if redness and induration were less than 5 x 5 mm. in size and was read twenty-four to thirty-six hours after injection. In epidemics of infectious hepatitis, 97 per cent of those with a history of jaundice had positive tests. In contrast, only 11 per cent of child-

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ren without history of exposure to hepatitis had positive tests. It is of interest that 35 to 40 per cent of patients with known cases of homologous serum hepatitis had positive tests — a percentage approximately the same as that found in skin testing of a random population of the same age. Stokes believes that this is additional evidence that infectious hepatitis virus is probably antigenically different from the virus of homologous serum hepatitis.

Recently, Drake et al.[8] suggested that the skin test might alter individual susceptibility to the hepatitis virus. In a closed institution where infectious hepatitis had been endemic, they found that in the year after testing, only 5 cases of hepatitis with jaundice developed in 320 children (1.6 per cent) who had been tested, whereas 112 cases of hepatitis with jaundice developed in 825 children (13.6 per cent) who had not been tested. Among the former, 176 had negative skin tests and therefore were presumably susceptible. They concluded that the skin test had altered susceptibility. The material used had not been tested by the oral route in volunteers, and it is possible that the virus had not been completely inactivated by ultraviolet light and was thus capable of conferring active immunity.

It is unfortunate that no comparable data on either the passage of infectious hepatitis virus or the use of the skin test have been published by other groups. Our own limited experience with skin testing using material supplied by Stokes was very disappointing; it is pointed out that active virus may have been lost in the course of passage through chick embryos,[8] thus accounting for unsatisfactory lots of antigen, and that the skin-test antigen is labile and deteriorates rapidly upon storage at 4°C., adding further obstacles to the production of a standard antigen. It appears that this work, especially the findings regarding active immunity, requires further investigation and confirmation. However, the preliminary published data are impressive and, if confirmed, represent an important new tool in the study of viral hepatitis.

Laboratory Tests

The flocculation tests continue to be the most important laboratory procedures in the diagnosis and management of hepatitis. In evaluating some of the newer technics, Maclagan[9] points out that the zinc sulfate turbidity test behaves in much the same way as the thymol turbidity test and that the ammonium sulfate test has a smaller range of deviation than either the thymol turbidity or the zinc sulfate test. Armas-Cruz et al.[10] suggest that the flocculation tests represent not only quantitative changes in the protein fractions, but also qualitative changes. Gamma globulin from the serum of patients with infectious hepatitis shows a greater flocculation potency than that obtained from normal serum or from serum of patients with obstructive jaundice. Both Weller[11] and Hsia and Gellis[12] recently pointed out that flocculation tests are unreliable in infants under six months of age. This may be due to the deficiency of gamma globulin that appears characteristic of that age group. Serial bilirubin determinations appear to be more useful than flocculation tests in this age group.[12]

Simplification of the technic for determining serum cholinesterase[13] has permitted application of this test to the study of hepatitis and liver disease. In general, serum cholinesterase tends to decrease early in acute hepatitis and regularly increases as the patient convalesces.[14, 15] Matassarin and Delp[16] and Peterson[17] have suggested the measurement of serum iron as a test of liver function. They point out that serum iron becomes elevated during hepatocellular damage and decreases after recovery. Selman[18] has reported extremely low antithrombin titers during severe homologous serum hepatitis. He believes that they are representative of centrilobular necrosis of the liver. Bjørneboe, Hamburger and Jersild,[19] in studies concerning steroid metabolism in liver disease, found that female patients with hepatic disease excreted a higher proportion of ingested estrogens than controls, whereas male patients with acute hepatitis excreted small amounts of 17 ketosteroids as compared with controls.

Electrophoretic studies on the serums of patients with acute hepatitis have shown elevations of the beta and gamma globulin fractions and depression of the serum albumin fraction.[20-24] Generally, there appeared to be close correlation between these changes and positive flocculation tests. Watson and his associates[25] and Sutherland and Bollier[26] demonstrated that the coproporphyrins are increased in the urine during the acute phase of hepatitis, and this increase often persists to some degree for considerable periods after the disappearance of jaundice and after the usual liver-function tests have returned to normal. The increase is limited largely to Type 1 isomer, the Type 3 isomer remaining within normal limits. The mechanism of abnormal coproporphyrin excretion in liver disease is poorly understood at present and requires further study.

One of the most promising new technics for the study of liver disease is the direct measurement of the excretion of specific amino acids in the urine by means of paper-partition chromatography. Dent and Walshe[27] have shown that in infectious hepatitis there is an increased excretion of both the numbers and quantity of amino acids early in the disease. They believe that, in severe liver disease, a tissue autolytic process results in the breakdown of whole proteins into the common amino acids, which are rapidly liberated into blood and urine. The kidney apparently plays no part in these changes since the excess of amino acids in the urine merely reflects the raised levels in the plasma.

Epidemiology

Interesting epidemiologic data were obtained by Capps and his co-workers[20-21] from an epidemic of infectious hepatitis in an orphanage for infants and small children. Among the significant findings was the observation that the transmission was apparently from child to nurse by the fecal-oral route, and airborne spread did not occur. Student nurses, in whom the incidence of the disease was high, ate the same food, drank the same water and, in some cases, lived on the same floor of the building as a group of maternity patients, in whom the disease never developed. The only difference between the two groups was that the student nurses handled the children, among whom hepatitis was endemic, whereas the maternity patients did not. Simple revision of nursing technics resulted in a dramatic elimination of new cases among the student nurses. Furthermore, a single dose of gamma globulin (0.06 cc. per pound of body weight) was given to all new student nurses for eight months. During this time and for a year afterward, only 1 case of hepatitis developed among the 36 girls treated, whereas the incidence was 32 per cent among the student nurses before and 45 per cent in the control group after this period. Since the passive immunity conferred by gamma globulin is a relatively short one, the most probable explanation for the low rate of the disease in the nurses receiving gamma globulin is that inapparent infections developed during the declining phase of their passive immunity, thus conferring an active immunity. Finally, although few children under three years of age had jaundice, it was believed that 80 per cent of the children were eventually infected.[20] The diagnosis in these children was made on the basis of positive liver-function tests, skin tests, demonstration of virus in the stools of 2 children through the use of adult volunteers and epidemiologic evidence of infection. The epidemic among the children could not be controlled by improved nursing technics or isolation of the children who were known to have active disease.

Except for possible active immunization by the skin test, which requires further confirmation,[9] gamma globulin remains the only effective agent in the prophylaxis of infectious hepatitis. Stokes and his associates[22] recently suggested that as little as 0.01 cc. per pound of body weight is effective in preventing infectious hepatitis. They found in one epidemic that 45 cases of hepatitis with jaundice occurred in 83 persons who served as controls, whereas only 3 cases of hepatitis occurred among 106 children and adults who had received gamma globulin, symptoms developing nine days, eighteen days and seven months, respectively, after the patients had received the gamma globulin. The authors concluded that prolonged protection in inmates of the three institutions from a single dose of gamma globulin despite continued intimate exposure must have been due to active immunity, and that waning passive immunity afforded the opportunity for inapparent or subclinical infections among the inoculated groups that resulted in active immunity superimposed on passive immunity, or in the words of the report, a "passive-active immunization."

Brooks et al.[23] showed that in 14 out of 29 families with an initial case of infectious hepatitis, hepatitis with jaundice developed in 1 or more additional members of the family, suggesting a high incidence of transmission of the virus among members of a family. The incidence appeared particularly high among children under fifteen years of age, hepatitis with jaundice occurring in 18 out of 51 exposed children. The same study demonstrated that only 1 of 55 adults and children given gamma globulin in 17 other families manifested hepatitis. In that case, the hepatitis developed only two days after the gamma globulin had been given. One can therefore conclude that gamma globulin is effective in preventing the spread of hepatitis in sporadic outbreaks not only within families but also in closed institutions. Studies using the dosage of 0.01 cc. per pound of body weight in alternate members of families exposed to infectious hepatitis are in progress.[24] The initial data suggest that this dosage is effective in preventing spread of the disease within families. It will be important in the future to determine if smaller doses may serve to attenuate the disease since prevention during childhood may not be desirable.

Clinical Studies

Little has been added to the clinical picture of hepatitis during the past five years. Leibowitz[25] found that 8 out of 11 smokers noted a definite complaint of distaste toward smoking as an early symptom of viral hepatitis; he offered no explanation for this interesting symptom. Fog,[26] in a study on food histories obtained from female patients with hepatitis and normal controls, observed no correlation between the severity of hepatitis and protein intake, but reported a statistically significant correlation between the use of laxatives and the severity of the disease. Leibowitz and Gorman[27] and Thorling[28] reviewed the nervous and mental changes in acute viral hepatitis. Central and peripheral nervous-system complications are rare, and psychotic reactions are not described. In the small group of fatal cases, nervous and mental symptoms are common and may dominate the terminal picture. Autopsy studies revealed a mild nonspecific encephalopathy and occasionally a mild form of meningoencephalitis.

Salvesen and Lödöen[29] described their clinical experience with infectious hepatitis during the war years in Norway. In a total of 40 cases reported, 26 patients had malignant hepatitis; 88 per cent of these were women. Of these 4 recovered, 3 had chronic hepatitis, and 19 died. Death occurred

during the first year in 14 patients. Clinically, glossitis, polyneuritis, ascites and esophageal varices were prominent findings; the majority of patients were over forty years of age. After analyzing the data, the authors concluded that malignant hepatitis probably differs in no way from hepatitis occurring in peacetime, but is more severe because of poor nutrition during the war. Ipsen,[40] reporting a similar series from Denmark, suggested that women over forty years of age with hepatitis have a prolonged and frequently fatal course because of inability of the liver to regenerate after an injury such as that caused by infectious hepatitis. Snavely[41] has written an excellent review of the pathologic physiology that leads to fatal hepatitis and corresponds well with the clinical descriptions given.

Denber and Leibowitz,[42] Domenici[43] and Zimmerman and Thomas[44] described sporadic cases of virus hepatitis without jaundice. The most frequently encountered symptoms were fatigue, anorexia, abdominal pains, headache and nausea. Liver tenderness and enlargement were found in the majority of the patients, and the flocculation tests were positive in three fourths of the cases tested. Most of the patients recovered within four months, but a few continued to show symptoms a year after the onset of illness. Clinically, hepatitis without jaundice may be difficult to differentiate from infectious mononucleosis. Leibowitz[45] has shown that heterophil-antibody titers are within normal limits in infectious hepatitis after absorption with guinea-pig kidney and beef red cells and that this test is a reliable one in the differentiation of hepatitis and infectious mononucleosis.

Evidence continues to accumulate that a certain percentage of the cases of acute hepatitis will eventually become chronic and progress to cirrhosis. Post et al.[46] reported a follow-up study of 114 patients with acute hepatitis. In the study of sequelae, gastrointestinal symptoms were the most common complaints. When they persisted for nine to seventy months after the acute illness, they were usually associated with chronic liver disease. Jaundice, palpable liver and spider angioma were the most common physical signs associated with chronic liver disease. Elevated icteric index and bilirubin levels and positive cephalin-cholesterol flocculation were the most commonly encountered laboratory tests. Of 44 patients with evidence of sequelae, 29 had one to three recurrences of jaundice, none had chronic jaundice, and 6 had prolonged convalescent states. Post and his associates found that recurrent jaundice was compatible with normal liver physiology fifty-six months after the acute illness, but frank cirrhosis of the liver could also occur fourteen months after the initial illness. In a similar study of 100 patients in a Veterans Administration hospital, Koszalka and his co-workers[47] found that 3 patients showed definite transition from acute hepatitis to portal cirrhosis. They also pointed out that chronic hepatitis may simulate a psychoneurosis and that 10 per cent of the patients were admitted to the hospital with such a diagnosis. Warthin and Dalrymple,[48] reviewing the concept of chronic hepatitis, suggested that its development is favored by several factors: age, incompleteness of treatment, severe complications, bacterial infection and severity of the initial attack. Insidious onset of symptoms and marked severity of the initial attack appear to favor chronicity. Alcohol during the convalescent phase and the complication of a severe bacterial infection are additional factors.

The rationale of complete bed rest in the management of patients with viral hepatitis has been tested by Swift et al.[49] They found that when patients whose total serum bilirubin measured 3.0 mg. per 100 cc. or more were given a period of graduated exercise, the mean duration of the disease was two weeks longer than that of control patients kept at bed rest. When the total serum bilirubin measured less than 3.0 mg. per 100 cc. the duration of convalescence was apparently not prolonged by exercise, regardless of the age of the patient or severity of the disease. Because of the difficulties in maintaining children at rest, we have permitted gradual activity after the bilirubin level falls below 3.0 mg. per 100 cc. in about 100 children with acute hepatitis, with no apparent ill effects or delay in recovery.[50]

Recent studies of dietary management of patients with hepatitis continue to show that total caloric intake appears more important than the proportion of fats, proteins and carbohydrates in the diet. Gertzen[51] has compared the response of patients on high-fat, high-protein and high-carbohydrate diets and found no statistical difference in the duration of illness. Ström[52] has studied the effect of added methionine to the diet of patients with hepatitis. Although he noted that there were fewer patients with increasing bilirubinemia after admission to the hospital and somewhat earlier return to normal as compared with the untreated patients, the differences were not statistically significant and certainly not dramatic.

A number of reports have appeared on the use of the newer antibiotic agents in the treatment of acute and chronic hepatitis.[53-62] It is assumed that the beneficial effects of these drugs are due to their detoxifying action on the intestinal flora on oral administration and to their action on bacteria in the portal circulation or liver when they are given intravenously. To date, the results, with the possible exception of patients in hepatic coma, have not been impressive. Studies on larger groups of patients are indicated before any definite conclusions can be drawn.

Similarly, the reports on the use of ACTH and cortisone in the treatment of hepatitis are not impressive,[63-68] and trials on larger numbers of cases are needed. Ducci and Katz[65] were able to reverse the process in 2 cases of fulminating hepatitis in

coma apparently by the use of cortisone and antibiotics, and it is possible that steroids inhibit the inflammatory reaction in the liver. Further investigations into the use of these agents are undoubtedly necessary.

Transplacental Transmission

During the past two years the problem of infectious hepatitis in early infancy and the possibility of transplacental transmission of the virus have aroused great interest. In 1951 Stokes and his associates[70] reported a series of 12 infants in whom hepatitis developed in the first two months of life. The pathologic findings of 6 of those who died were similar to those described in older children and adults, but with certain peculiar and somewhat specific morphologic changes. Serum hepatitis virus was apparently transmitted to human volunteers by injection of the blood from one of the infants who died and also from his mother. In analyzing 156 infants with prolonged obstructive jaundice, Hsia et al.[71] found that 30 cases (19 per cent) were due to inspissated bile, the etiology of which was unknown. Craig and Landing[72] analyzed the pathologic sections in these cases and found them all to be similar to changes seen in viral hepatitis in older children and adults. It appears that viral hepatitis in infancy is seen more frequently than hitherto believed and must be considered in the differential diagnosis of obstructive jaundice in that age group.

Whether the agent responsible for the pathologic changes is transmitted across the placenta remains to be proved. Hsia, Taylor and Gellis,[73] in a follow-up study of a group of women with known infectious hepatitis during pregnancy were unable to find any evidence of hepatitis in their offspring. Zondek and Bromberg,[74] in a follow-up report on a similar group for a relatively short period, also failed to demonstrate any changes in the children. It appears likely, therefore, that transplacental transmission of infectious hepatitis virus is quite rare. In view of the fact that almost all the mothers of young infants with hepatitis were asymptomatic and free of jaundice during pregnancy, it is possible that they were carriers of homologous serum hepatitis virus, which may persist in the blood stream for many years without symptoms. The observation by Hessler[75] of death from hepatitis in 3 infants born in succession of the same mother suggests that the mother was an asymptomatic carrier. Similarly, the development of juvenile cirrhosis in 4 siblings during infancy reported by Adams and his co-workers[76] adds evidence to that concept.

Homologous Serum Hepatitis

Incidence

During the past five years there have been several new surveys regarding the incidence of homologous serum hepatitis after the use of blood and blood products. McGraw, Strumia and Burns[77] report 20 cases (2.2 per cent) of "possible hepatitis" and 12 cases (1.3 per cent) of "probable hepatitis" in 910 patients who received transfusions. Of 382 patients who received blood alone, only 1 (0.3 per cent) had "probable hepatitis." Of 528 patients who received plasma with or without whole blood, 10 (1.9 per cent) had "probable hepatitis." Robinson et al.[78] found that 6 of 621 (0.96 per cent) recipients of pooled plasma contracted homologous serum hepatitis. Ratnoff and Mirick,[79] in a survey at the Johns Hopkins Hospital, found that approximately 1 out of every 7 patients hospitalized with acute hepatitis during a twelve-year period had received blood or a blood fraction five weeks to five months before the onset of disease. Twenty per cent of 183 patients with hepatitis had had a test or had received injections other than blood or arsenicals five weeks to five months before the onset of their illness, whereas only 8 per cent of 258 patients without hepatitis who served as controls had had similar tests or injections. The probability that this difference occurred by chance is less than 1:100, emphasizing the importance not only of the administration of blood or plasma in the transmission of hepatitis but also of the hazard of any procedure in which the skin is pierced.

Lehane and his associates[80] compared the incidence of homologous serum hepatitis after transfusion of large pools of plasma (each pool containing no fewer than 300 donors), small pools of plasma (each pool containing less than 10 donors) and whole blood. A diagnosis of homologous serum hepatitis was made only if jaundice occurred one to six months after transfusion. There was no history of contact with infectious hepatitis and there was no other explanation for the jaundice. The incidence of hepatitis was 11.9 per cent after transfusions with plasma from large pools, 1.3 per cent after transfusions from small pools and 0.8 per cent after transfusions of whole blood. The findings suggest that at least 0.35 per cent of donors are probable carriers of the icterogenic virus, arguing strongly for the use of whole blood or small plasma pools as opposed to plasma pools obtained from large numbers of donors. Lehane et al. noted that only 1 case of homologous serum hepatitis occurred in 214 children under ten years of age given transfusions of blood or plasma. In contrast, the attack rate was 5.7 per cent for those ten to twenty years of age, 6.8 per cent for those twenty to thirty years of age, 7.1 per cent for those thirty to forty years of age, 9.1 per cent for those forty to fifty years of age, 9.3 per cent for those fifty to sixty years of age, 8.1 per cent for those sixty to seventy years of age and 2.2 per cent for those seventy to eighty years of age. This confirms the previous impression that children are relatively resistant to homologous serum hepatitis[81, 82] but highly susceptible to infectious hepatitis.[82, 83]

Blood Fractions and Homologous Serum Hepatitis

Recent studies have confirmed earlier impressions that albumin and gamma globulin fractions are extremely unlikely to play a role in the transmission of homologous serum hepatitis. Paine and Janeway[86] investigated 237 patients who received human albumin intravenously in four Boston hospitals during 1950 and 1951. The albumin had not been subjected to ultraviolet irradiation and was prepared from dried plasma that had been stored for a considerable time. After recipients who died within five months of the infusion and those who had cirrhosis or other liver disease had been excluded, 33 remained who received albumin only and 93 who received blood or plasma in addition to albumin. No case of homologous serum hepatitis occurred in the former group. Since the albumin was prepared from lots of approximately 500 units of 25 gm. each, the number of original donors represented in each unit was at least 2000. If the incidence of carriers is about 0.2 per cent with the current rigorous screening of donors, it may be calculated that a single unit of albumin probably contains material from at least 1 infectious donor. The findings suggest that the administration of human albumin does not carry the risk of homologous serum hepatitis that exists with the use of pooled plasma or serum and perhaps has less risk than plasma or whole blood obtained from a single donor.

Cockburn et al.[88] have presented striking data on the incidence of homologous serum hepatitis after the administration of gamma globulin. In a study of measles prophylaxis, plasma collected from 60 donors was fractionated except for a small amount that was dried and issued unfractionated. The unfractionated material was inoculated into 10 children and within fifty-seven to sixty-four days of inoculation, hepatitis developed in 7 of the 10, 3 of whom died. Of the 58 persons who received the gamma globulin fraction of the plasma pool, only 1 contracted hepatitis, seventy-four days after the material was given. The authors conclude that gamma globulin is much less icterogenic than plasma or serum, but is probably not wholly free from the risk of hepatitis. These findings are in accord with those of Janeway,[86] who investigated 869 persons injected with gamma globulin and found no incidence of hepatitis, and Ordman, Jennings and Janeway,[87] who found only 1 case of jaundice among 400 recipients of gamma globulin.

Other blood products are apparently capable of transmitting hepatitis virus. Hepatitis has followed administration of Cohn's Fraction I, which was distributed in the dry state and which cannot be heat treated after denaturation.[88] Lesses and Hamolsky[89] reported 22 cases of homologous serum hepatitis that followed the use of human thrombin, which is derived from pooled plasma and directly prepared from Cohn's Fraction III. Hsia et al.[90] recorded 4 cases in 16 children who received Cohn's Fraction IV prepared from pooled post-partum plasma used in the treatment of rheumatoid arthritis. Whether the apparently increased incidence is the result of removing the protective effect of gamma globulin from the plasma pool remains to be determined.

Source of Outbreaks

Outbreaks of homologous serum hepatitis originating from a common source continue to appear in the literature. Borensztejn[91] reported hepatitis in 216 patients under treatment for venereal disease. The disease was apparently spread by syringes and needles and disappeared when these were washed in water, immersed in 5 per cent carbolic acid for three minutes and then boiled for twenty minutes. He believed that arsenic administration and protein deficiency played a secondary role in increasing the severity of the disease but could not be incriminated as causal agents. In a similar study, Sherwood[92] recorded an incidence of 44 per cent of syringe-transmitted hepatitis with jaundice in a group of hospitalized diabetic patients. The agent was apparently transmitted by the multiple-dose-per-syringe technic of administering insulin. The incubation period in this epidemic ranged from a minimum of sixty-four to a maximum of a hundred and six days. The use of a sterile syringe and needle for each patient greatly reduced the hazard of transmitting infected serum from patient to patient.

A number of reports have appeared on the incidence of homologous serum hepatitis among narcotic addicts.[93-96] In a survey conducted in New York City, the incidence appears to be increasing and occurs primarily in addicts under thirty years of age and of Negro or Puerto Rican origin. All are assumed to have acquired the disease through the common use of needles and syringes for administering morphine or heroin. Koteen and his associates[97] and Smith and Hall[98] recently reported the transmission of homologous serum hepatitis through the inoculation of blood containing malaria organisms for the treatment of syphilis. Smith and Hall were able to trace the patient who probably served as the source of icterogenic material. At least three outbreaks of hepatitis have been attributed to tattooing.[99-101] In an outbreak in Panama City, 18 of 26 patients were found to have been tattooed ninety-nine to a hundred and fifty-four days before the onset of their symptoms; 17 of the 18 had been tattooed by the same operator and had presumably acquired their infection from the same needle.

Prevention

Stokes et al.[102] have shown that gamma globulin, although not always effective in preventing homologous serum hepatitis, has protective properties against strains of this virus. In a hospital for battle casualties, two injections of 10 cc. each of gamma

globulin given at a thirty-day interval during the incubation period of the disease appeared highly protective. In two other general hospitals in which a single injection of gamma globulin was administered during the incubation period, decided prolongation of the mean incubation periods resulted in the two test groups. The single administration of gamma globulin apparently did not alter the incidence of homologous serum hepatitis despite its effect on the incubation period. The authors suggest that the effect of gamma globulin may be based on a purely qualitative relation between the numbers of viral bodies and the amount of inhibiting factor of the gamma globulin. Thus, two doses of 10 cc. given at a thirty-day interval may be sufficient to neutralize all viral particles present, whereas one dose of 10 cc. may reduce the amount of virus to a point from which the relatively slow process of multiplication has to be repeated. Thus, the prolongation of the incubation period may be solely the result of delay in the increase of viral particles to a point at which clinical disease may develop.

Despite the lack of clear-cut proof of effectiveness against homologous serum hepatitis it is our opinion that gamma globulin should be given prophylactically to personnel receiving cuts or skin injections from instruments or needles that have been used in patients with hepatitis. Three injections of gamma globulin at monthly intervals after such accidents are recommended.

Blanchard and his co-workers[108] have presented evidence that ultraviolet rays may be effective in inactivating the virus of homologous serum hepatitis. Of 15 volunteers who received nonirradiated icterogenic serum, hepatitis with jaundice developed in 3, and hepatitis without jaundice in 1, and 3 had presumptive hepatitis. Of 11 volunteers who received irradiated icterogenic serum, none contracted hepatitis. Since the publication of that study, numerous papers[104-108] have appeared reporting cases of hepatitis after the use of ultraviolet-irradiated plasma or serum. Under the conditions employed, ultraviolet irradiation appears unsatisfactory as a method of eliminating the virus.

Hartmann and his associates[109] and Steele[110] have recommended the treatment of plasma or blood with nitrogen mustards, particularly methyl-bis amine hydrochloride. It is difficult to evaluate this work at present since no large-scale studies on the possible toxic effects of these agents and the incidence of homologous serum hepatitis with their use have been undertaken. Allen et al.[111] suggest that plasma should be stored in the liquid state without preservatives at temperatures of 80 to 96°F. for three months or longer. They consider these conditions less favorable for the preservation of virus, and maintain that homologous serum hepatitis is rarely encountered after storage in this manner. Of 864 patients given such plasma, homologous serum hepatitis developed in 3, all of whom had received whole blood or lyophilized plasma in addition to the pooled plasma. No jaundice occurred in any of the 212 patients who received the plasma alone. During the same period of study, at least 14 to 17 of 6503 patients who received whole-blood transfusions only manifested jaundice.

It appears that the ideal procedure for the destruction or neutralization of the virus of homologous serum hepatitis has yet to be found. Until an effective method becomes available the use of whole blood or plasma from a single donor appears to be the best solution to limiting the spread of hepatitis through transfusions. It is also clear that albumin and gamma globulin are relatively innocuous products and that other fractions prepared from pooled plasma are highly icterogenic. In the event of known contamination with the virus, gamma globulin in large and repeated doses should be given in the hope that it will prevent the disease.

Homologous Serum Hepatitis as an Occupational Hazard

Increasing attention is being given to homologous serum hepatitis as an occupational hazard to medical personnel. Trumbull and Greiner,[112] in a survey of four hospitals during a four-year period noted 16 cases among the personnel. These included 2 blood-bank aides, 1 blood-bank technician, 4 laboratory technicians, 2 operating-room nurses, 1 student nurse, 1 dentist, 1 intern, 3 surgeons and 1 pathologist.

The hazard appears especially great among laboratory technicians.[113] Kuh and Ward[114] report 7 cases of hepatitis occurring among workers in a commercial firm engaged in plasma fractionation. They believed that the virus gained entry through cuts and abrasions and through inhalation into the nasopharynx of plasma in powder form. Periodic injections of gamma globulin in exposed workers have apparently been effective in reducing the incidence of hepatitis although no details are given. Leibowitz et al.[115] cite a case of a forty-one-year-old nurse working in the blood bank of a large hospital in New York City who manifested hepatitis after pricking her finger. The New York State Workmen's Compensation Board, after formally hearing the case, decided that it was the result of an accident and that a causal relation had been established between the illness and the conditions of employment, and made an award in favor of the patient.

Two studies concerning the incidence of hepatitis among physicians have recently been reported. In a survey of hepatitis in physicians in Sweden by means of a questionnaire, of 3802 physicians who answered the questionnaire satisfactorily, 531 had at some time suffered from one attack of hepatitis and 22 reported having had the disease more than once.[116] In many cases, hepatitis had developed late in life. The rate was higher among physicians in hospital practice than among those in general

practice. It was higher among hospital physicians who operated than among those who did not. In Denmark, a similar survey among 4700 physicians, 2000 lawyers and a large number of hospital nurses, as well as the employees of three important industrial concerns revealed there was a significantly higher incidence of hepatitis among physicians in every age group as compared with persons in other professions or occupations.[117] For lawyers and physicians, the rate reached its maximum between the ages of forty and fifty, whereas the maximum was reached ten years earlier by persons in other occupations. Among the 463 physicians who stated that they had suffered from hepatitis in adult life, 160 had the disease during hospital work whereas in 100 cases the disease was thought to have been contracted in ordinary medical practice. Altogether, the frequency of hepatitis after eighteen months was 8.4 per cent for physicians, 6.8 per cent for nurses, 7 per cent for lawyers and 3.9 per cent for industrial workers. No medical specialty appeared particularly susceptible to hepatitis, and neither laboratory workers nor operating-room personnel seemed to be particularly liable to this disease, in contrast to the Swedish survey.

Two reports on the transmission of homologous serum hepatitis through dental equipment have appeared in the German medical literature.[118, 119] Gellis and Hsia,[120] in a survey among dentists in Massachusetts, found that 8.5 per cent reported having had hepatitis. In comparing the age distribution of the dentists who reported hepatitis with the reported cases in Massachusetts, the dentists appeared to have a greater incidence of the disease in the age group from twenty to forty-five years, suggesting a possible relation to occupation.

Other Forms

A number of other agents are known to cause hepatitis and frequently simulate viral hepatitis in their signs and symptoms. Infectious mononucleosis is often manifested by a history of anorexia, vomiting, abdominal pain, malaise and enlarged, tender liver, and skin and scleral icterus. Bennett et al.,[121] Jordan and Albright[122] and Watson and his associates[123] have found liver-function tests to be positive in adults with the disease, and Hsia and Gellis[124] have shown that 84 per cent of children with a heterophil-antibody titer of 1:56 or higher showed positive liver-function tests whereas none of the patients who were assumed to have infectious mononucleosis but who subsequently proved not to have the disease had positive tests. This is not surprising since Sterling[125] has shown the electrophoretic pattern to be similar in the two diseases and Custer and Smith[126] and others have described changes in the liver in infectious mononucleosis similar to those seen in viral hepatitis. Leibowitz and Brody[127] reported a case of infectious mononucleosis with hepatitis developing into frank cirrhosis.

Hepatitis associated with brucellosis is discussed by McCullough and Eisele.[128] Initial biopsy showed severe hepatitis with numerous areas of focal necrosis and extensive loss of liver cells. The patient had a progressively downhill course, with an enlarged, nodular liver, and persistent and progressive abnormalities of liver-function tests. A second biopsy two years later showed markedly increased fibrous tissue, deranged structure and nodular regeneration. These changes progressed after the brucellosis had become quiescent, and the patient was apparently cured.

Zuelzer and Stulberg[129] recently described a series of young infants who were found to have fulminating hepatitis and visceral disease due to herpes simplex. More than 70 per cent of the liver parenchyma was estimated to be destroyed, the areas of necrosis involving many lobules. Hepatic epithelial cells adjacent to necrotic zones invariably contained intranuclear inclusions characteristic of herpes simplex. In 1 infant the authors were able to isolate the virus of herpes simplex, confirming the clinical and pathological evidence of hepatitis due to herpes virus.

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MEDICAL INTELLIGENCE

AN ORIGINAL APPARATUS FOR COLOSTOMY IRRIGATION*

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DONALD B. ALDERMAN, M.D.‡

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THE commonly employed method of colostomy irrigation is unnecessarily protracted and unpleasant. Various irrigating apparatus have been tried by us and have proved unsatisfactory because of leakage and confinement of the patient to the toilet bowl for long periods. We have designed an apparatus that is inexpensive, easy to clean and leakproof; it allows visualization of the colostomy stoma during the irrigation and can be adjusted to fit the size of the stoma.

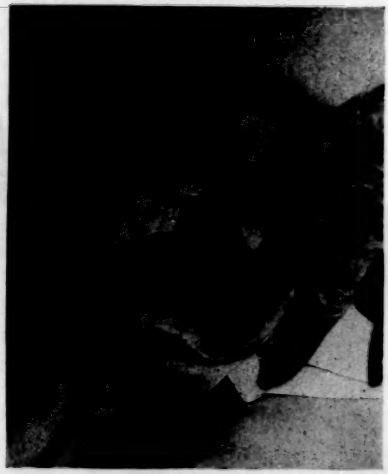

FIGURE 1. *Photograph of the Apparatus in Place.*

The basic elements are a Paragon colostomy disk and belt,§ and a long, pliable open-end tube of latex rubber with a side arm for insertion of a urethral catheter passed through an infant's bottle nipple. The central portion of the colostomy disk is cut out with a pair of scissors, and the size of the aperture made to conform to the colostomy.

FIGURE 2. *Occlusion of the End of the Tube by a Clamp.*

The thin latex tube is attached to the flange on the disk by means of a heavy elastic band supplied with the disk. The disk is held to the body by the belt. Irrigation is carried out in the sitting position by insertion of the catheter and nipple through the side arm (Fig. 1). The use of the nipple helps prevent leakage while the fluid is being injected from a can supported about 3 feet above the level of the colostomy. Once the proper amount of irrigating fluid, usually 1 liter, has been injected, the catheter and nipple are either kept in place temporarily, to prevent too rapid expulsion of the fluid, or removed immediately, depending on the characteristic action of the colostomy. When the catheter is removed, a rubber band is employed to close the side arm. Drainage into the toilet bowl via the long tube then occurs. If expulsion of the fluid is delayed or if there is continued expulsion over a protracted period, as usually happens, the end of the tube is wrapped with a rubber band to close

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§The entire apparatus can be bought from Thomas Fazio Laboratories, 339 Auburn Street, Auburndale 66, Massachusetts.

it firmly. Some patients prefer occluding the end of the latex tube with a broad, screw-type clamp (Fig. 2). In this manner, shaving or other functions may be carried out while the patient is awaiting completion of expulsion, and less time is lost. Most patients employ two 1-liter irrigations and require about forty-five minutes for the entire process. It is estimated that the patient employing this apparatus could devote two thirds of that time to the pursuit of activities other than the care of the colostomy. The latex tube is easy to clean and lasts indefinitely if washed with warm water and powdered after each use. The materials used are inexpensive and completely nonbreakable and should not require frequent replacement. Leakage has been eliminated.

SUMMARY

A simple, inexpensive and efficient colostomy irrigation apparatus is described.

DOCTORS AFIELD

John Locke

R. A. NORTON

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THE seventeenth century was a remarkable period for England. Colonists moved out to occupy the new world discovered in the previous century; Puritan businessmen at home prospered and gradually gained political power, and the ages of blind faith and of fanatic zeal were passing away, to be replaced by tolerance and critical doubt. John Locke, a modest, pious and prudent man, lived among these changes and helped to direct them.

He was born three hundred and twenty-one years ago near Bristol, the son of a country attorney. The Civil War was fought during his childhood, but his education took place uninterruptedly at the Westminster School and Christ Church, Oxford. At both institutions he rebelled against the traditional scholastic discipline, a heritage of medieval Aristotelian thought. The following comment is by Anthony Wood, one of Locke's schoolmates at Oxford[1]:

> This same John Locke was a man of turbulent spirit, clamorous and discontented; while the rest of our club took notes deferentially from the mouth of the master, the said Locke scorned to do so, but was ever prating and troublesome.

Locke took his bachelor's degree at the age of twenty-three, and his master's three years later. He stayed at Oxford to lecture in Greek, rhetoric and moral philosophy. In spite of the sterility and sophistry of the schools at that time, they furnished him leisure for his own investigations and contact with stimulating men. In this period Locke suffered a serious attack of love. After exchanging tender letters with a certain young lady, however, he recovered, and remained a lifelong bachelor.

A temporary position as secretary in the diplomatic service took him away from Oxford. He accompanied the ambassador to the court of the Elector of Brandenburg during one winter, carefully recording in his journal the events of life outside England. Returning to Oxford still undecided about a career, he refused a second diplomatic post and also an offer that would have led him into the clergy.

Interest in experimental research was drawing him into medical work. In 1668 Locke became a

John Locke (*Reproduced from* The Harvard Classics,[2] *with the Permission of the Publisher*).

fellow of the Royal Society, only six years after the founding of that famous body. Though lack of a medical degree did not bar a physician from practicing in seventeenth-century England, he usually sought to obtain one either by following a prescribed course of university studies or by royal dispensation after accomplishing a certain amount of independent work. When Locke, already thirty-eight years old, applied for an M.D. under the latter plan, his petition failed, rather irrelevantly, because of his liberal religious views. Four years later, after considerable practice with his friend, Dr. Thomas, he obtained the degree of bachelor in medicine and was thereafter known as "Doctor Locke."

His medical practice led to what was perhaps the most decisive single event of his life, his introduction to the powerful Lord Ashley. It came about this way: Lord Ashley planned to spend a few days with his son at Oxford and wanted to drink medicinal waters there at the same time. He wrote to Dr. Thomas, asking him to provide the waters. The doctor, obliged to go out of town, turned his patient over to Locke's care. Ashley "in his wonted manner, received him very civilly," wrote Lady Masham later, and "with great easiness; and when Mr. Locke would have taken his leave of him, would needs have him to stay supper with him, being much pleased, as it soon appeared, with his conversation."[2]

Locke saw Lord Ashley frequently after this, and indeed moved to his house the next year as medical adviser and confidential agent. His services to his host and the Ashley family were numerous and varied. In his first year with them, Locke consulted various other doctors and performed on Lord Ashley a difficult operation for the removal of an abscess in the chest. He kept the wound open with a silver tube, and the operation is said to have saved Ashley's life. The political satirists of the day delighted hugely in the silver tube.

Lord Ashley soon was created the first Earl of Shaftesbury and rose to become Lord Chancellor of England. He appointed Locke secretary of presentations and secretary of the Board of Trade. Locke also continued to tutor Ashley's son, the future second Earl of Shaftesbury. So completely did the family rely on him, that Locke was entrusted with the mission of finding a wife for his pupil. The match he engineered was a happy one, and in due time he assisted at the delivery of the third earl. His major philosophical work, the *Essay Concerning Human Understanding*, was begun in these busy days, but it is significant that it was not published for another fourteen years. In accord with his cautious temper, he waited and made many revisions in the work. The intervening years were stormy ones.

Shaftesbury lost office after a year, and Locke went to France in search of health. He suffered from chronic consumption and frequent attacks of asthma. As he wrote to a friend[3]: "My health is the only mistress I have a long time courted, and is so coy a one that I think it will take up the remainder of my days to obtain her good graces and keep her in good humour." In France he served as a tutor and was private physician to the wife of the English Ambassador at Paris. Shaftesbury regained power for a short while and recalled Locke to England. He reluctantly returned home, but within three years Shaftesbury's political fortunes collapsed, and they both had to flee to Holland. Locke had not encouraged Shaftesbury in any of his intrigues, but it was dangerous to remain at the mercy of an angry and tyrannical government.

During his voluntary exile he traveled and visited scholars at their work. He met the theologian, Limborch, and "was present, by invitation of Peter Guenellon, the principal physician of Amsterdam, at the dissection of a lioness which had been killed by the intense cold of the winter."[4] When the English government demanded of the Hague that Locke and other "subversives" be given up, Locke had to go into hiding. William Penn subsequently offered to obtain a pardon from James II, but Locke refused and said that he was conscious of having committed no crime. After the Revolution of 1688, Locke returned to England in the same fleet with his future sovereign, the Princess Mary of Orange.

When again in London, he continued and completed his writing. The *Essay*, published in 1690, aroused lively controversy at once. Its empirical psychology was influenced in part by Bacon's insistence on inductive methods. Locke realized, as Descartes had, that the medieval, Thomistic conception of the world was no longer valid. Unlike Descartes, he did not rely solely on the laws of mathematics for building his system, but used the experimentally verified theories of Newton's universe. Although many of Locke's conclusions have been put into practice successfully, his theory of knowledge was essentially self-contradictory, as Bishop Berkeley and David Hume later pointed out.

Locke's writings stressed his vindication of individual worth and responsibility. *Two Treatises on Government* (1690) attacked the theory of divine right of kings and justified the Revolution of 1688. *Letters on Toleration* (1689) supported the right of the individual to follow his own conscience in religious affairs.

These and his other writings show the influence of Locke's medical training. His habit of physical experiment led him to look at phenomena as a succession of caused causes, as natural occurrences, rather than as supernatural events from a constant originating cause.

As his last public service Locke accepted membership in 1696 on the newly constituted Board of Trade, where his ideas on commerce and colonies were highly esteemed. More than once he asked leave to resign because of London's ill effect on his lungs, but the King persuaded him to remain for four years. King William, who was subject to the same sort of asthmatic complaint, asked Locke about his treatment of his own disorders. "The King, when he was told that a very strict abstinence afforded the only relief, acknowledged that the advice was very good, but, like other patients, did not resort to that disagreeable remedy."[5]

Locke retired to live at Oates in Essex with Lord and Lady Masham, his close friends since the Holland exile. He insisted upon paying 20 shillings a week for himself and his servant, and another shilling a week for feeding his horse. His favorite exercise was riding, and the neighboring cottagers

became familiar with his spare form passing on horseback on the rough roads. Although he had ceased to practice actively, his journal records the unusual cases that came to his attention.

During his closing years he occupied himself with writing a commentary on the Epistles of St. Paul. He became troubled with a swelling of the legs and finally, too weak to rise, asked Lady Masham to come to him. He thanked God he had passed a happy life but said he now believed all in this world was vanity and merely a preparation for a better state hereafter. He died the next day, in his seventy-third year.

Americans owe more to John Locke than they ordinarily realize. He had a profound influence on colonial political philosophy in the eighteenth century. The words of this ancestor of the American Revolution were widely quoted by the patriots and found their way into both the Declaration of Independence and the Constitution. He contributed new awareness to the fields of education, politics, religion, economics and philosophy. It is clear that his inquiring mind was prepared by the study of medicine for its great philosophical task in helping to shape the modern world.[6-8]

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39361

Presentation of Case

First admission. A thirty-year-old salesman was admitted to the hospital because of a severe ache in the right side.

The patient was well until five months before admission, when he "caught a virus infection" characterized by a steady ache across the back at the costal margin. This pain increased during the next three or four weeks, and may have been associated with slight fever, although the patient continued to work. Pain became more severe during the next few weeks and was worse in the right posterior and lateral aspects of the back. At this time he had a roentgenogram of the chest and was told he had an infection at the right lung base, although he did not have cough or sputum. When this x-ray film was subsequently reviewed by another roentgenologist, it was considered normal. The patient then had a week of fever of unknown degree and sweating but no chills. He was confined to bed for two or three weeks, during which the pain in the back gradually subsided. He had lost about 20 pounds during his illness. Two months before admission, approximately two weeks after the steady back pain subsided, a new pain developed in the right lateral aspect of the abdomen that had subsequently been present almost continually. This increased in severity and was worse at night although it did not keep him awake. The pain was sharp and steady, feeling like gas cramps. It was worse on motion or coughing, and with deep breathing felt like a binding sensation in the lower anterior part of the chest. On six or eight occasions he had transient associated pain in the right anterior shoulder. He could relieve the pain somewhat by grasping his side. A roentgenogram of the chest and a barium-enema examination two months before admission were said not to have shown any definite disease except for what seemed to be an unusual degree of spasm of the cecum. There were no pulmonary, gastrointestinal or urinary symptoms.

The patient had been in the South Pacific and had visited Naples during World War II.

Physical examination showed a well developed and moderately well nourished man who did not appear ill. He guarded the right side and winced with pain on deep breathing. The heart was normal. Expansion of the chest was diminished on the right. The diaphragm was higher on the right than on the left and moved 0 to 0.5 cm., with dullness, decreased breath sounds, voice sounds and tactile fremitus in the area. There was no rub. There was local tenderness over the lateral aspect of the right eleventh or twelfth rib close to the spine. No masses were palpable. The abdomen was normal.

The temperature was 99.5°F., the pulse 92, and the respirations 20. The blood pressure was 126 systolic, 84 diastolic.

Examination of the blood revealed a white-cell count of 21,200. Three days later the hemoglobin

was 13.0 gm. per 100 cc., and the white-cell count 15,800, with 85 per cent neutrophils, 8 per cent lymphocytes, 4 per cent monocytes and 1 per cent each basophils and eosinophils. Two stool specimens were negative for amebas.

Roentgenograms of the chest showed apparent splinting of both leaves of the diaphragm. The lung fields aerated well, however, and there was no elevation of either leaf of the diaphragm or evidence of changes beneath the right leaf. In a plain film of the abdomen there was a questionable loss of the properitoneal fat line on the right side. The right kidney was well delineated, and there was no change since a previous film three weeks before. A barium-enema examination was unsatisfactory.

On the second hospital day an oblique incision was made over the course of the twelfth rib extending downward and forward beyond its tip. The tissues overlying this area were definitely edematous. The major portion of the twelfth rib was resected, and the incision carried down through the bed of the rib into very thick, hard inflammatory tissue. During separation through this mass of tissue with scissors an abscess was broken into that contained not more than 30 cc. of nonodorous pus. A biopsy was taken and the wound packed with gauze. The biopsy was subsequently diagnosed by the pathologist as acute and chronic inflammation with granulation tissue. The patient continued to have temperature elevations to 99 to 100°F. during most of the hospital stay. He was discharged on the seventeenth day.

Second admission (about three weeks later). Since discharge he had felt well, and his wound had almost stopped draining. He entered the hospital for an interval appendectomy. Physical findings were as before. Urinalysis was negative. The hemoglobin was 11.8 gm. per 100 cc., and the white-cell count 13,400. At operation the appendix was found to be edematous and adherent beneath the ileocecal mesentery. The microscopical diagnosis was: appendicitis, subsiding. The wall of the appendix was greatly thickened and fibrotic. A few eosinophils, lymphocytes, and monocytes were present in the wall; the normal submucosal lymphoid tissue was almost absent. The patient was discharged at the end of a week.

Final admission (five months later). In the interval he had had a persistent draining sinus in the middle of the old wound but had felt well until three months before admission, when he noted the onset of fatigability, lack of ambition and daily temperature elevations to 99 or 100°F. In addition, he had been slowly and steadily losing weight in spite of active dietary efforts to gain weight. He did not have chills. In view of the persistence of symptoms he was admitted for further study.

Findings on physical examination were as at the time of the previous admissions. The temperature was 99.5°F., the pulse 110, and the respirations 20.

A urinalysis was negative. The hemoglobin was 11.0 gm. per 100 cc., and the white-cell count 18,700, with 88 per cent neutrophils, 8 per cent lymphocytes, 3 per cent monocytes and 1 per cent basophils.

On the second hospital day an operation was performed.

Differential Diagnosis

Dr. J. Gordon Scannell*: To summarize the important points in the history as given, the patient was a young man who had a subphrenic abscess that failed to heal and for which a primary source was not found. We are given the gross characteristics of the inflammatory response — namely, that it was an extremely proliferative process with little central necrosis and little pus. The pus had none of the characteristics of the ordinary infections of gastrointestinal-tract origin. We do not have a record of any culture of the pus. There is also no mention whether or not the patient was given antibiotics, but it is incredible that in this present day he did not have them. If he was given antibiotics, they may have altered the classic tissue response to the infecting organism.

May we see the x-ray films before going further?

Dr. Joseph Hanelin: The abdominal film is normal. There may be slight alteration in the thickness of the properitoneal fat line on the right, but it is questionable. The kidney outlines and psoas-muscle shadows are clearly defined. The chest examination is negative. The only positive roentgenographic observation is in the region of the cecum and ascending colon, which show considerable evidence of spasm. One of the barium-enema examinations was unsatisfactory because there was difficulty in filling the ascending colon and cecum. However, it was possible at times to fill the cecum and distend it to a reasonably normal contour, although at other times during the course of fluoroscopy, the cecum was markedly contracted and irritable. This film, which was a follow-up study of the gastrointestinal series, shows a fairly normal-looking small bowel to the ileocecal valve, without any evidence of a mass in that area.

Dr. Scannell: Do you see any evidence of a perforation or abscess cavity in the region of the cecum?

Dr. Hanelin: No.

Dr. Scannell: Our problem, then, is one of chronic infection with a persistent sinus. An abdominal sinus that fails to heal suggests an underlying tumor, an underlying foreign body, tuberculosis and a mycotic infection, of which actinomycosis is the most likely. This may be an oversimplification of the problem, but in a young patient with these x-ray findings I think it is a reasonably inclusive list.

The first condition on the list is carcinoma, and we have no evidence of a primary carcinoma in this

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patient. It is true that no intravenous pyelogram was done, but the urine was normal on several occasions, the kidneys were well visualized in the plain film of the abdomen, and there were no renal symptoms. Similarly, we have no evidence of a primary bowel lesion. The barium-enema examination was abnormal, but it did not suggest tumor and furthermore at the time of appendectomy the ascending colon was presumably explored and no evidence of tumor found. I should therefore be inclined to discard the bowel as a source of tumor. Furthermore, there was little to suggest a primary tumor of the liver in the absence of any clinical disturbance of liver function. Finally, there was little evidence of tumor of the lung, for the studies of the chest were virtually negative. There were no real respiratory symptoms, and a tumor of the lung rarely produces this picture. I am inclined, therefore, to think that the patient did not have carcinoma.

The second possibility is a retained foreign body. We might reconstruct the problem somewhat as follows. The patient may have had a subphrenic abscess secondary to a previous appendicitis that was not recognized. At the time of the first operation a small portion of denuded rib might have been left behind, and this might have formed a sequestrum. We cannot discard this completely as a possibility. Is there an x-ray film taken postoperatively?

Dr. Hanelin: I do not believe it was contributory.

Dr. Scannell: One would like to introduce some Lipiodol into this sinus and see if it leads down to a rib or a rib bed. However, I think it is unlikely that it would, for presumably the resection of the twelfth rib was done extraperiosteally so that there would be little likelihood of chronic osteomyelitis in a re-formed rib. We have no evidence of any other type of foreign body in the abscess.

The third condition that I mentioned is tuberculosis. To make this diagnosis we would have to have a positive culture or definite findings in the original biopsy. Tuberculosis was perhaps suggested by the fact that the cecum showed inflammatory changes. It is my opinion — I am not sure how accurate it is — that in the adult, tuberculosis of the cecum is almost always associated with an open chest lesion and that the patient is swallowing the organisms. In this patient there was no evidence of primary tuberculosis, and there is little reason to make that diagnosis on the subphrenic process, for the gross characteristics of the lesion were not those of a cold abscess or a tuberculous process.

We are therefore left with the diagnosis that I should like to select — namely, a mycotic infection, of which actinomycosis is the best bet. The gross description of the original subphrenic abscess sounds a great deal like actinomycosis. The original site in the appendicular region fits with that diagnosis, although I should expect more evidence of a local abscess in the region of the appendix. We have the note, however, that this appendix had been inflamed but was subsiding. The pathological diagnosis of subsiding appendicitis has always been somewhat of a mystery to me. Perhaps the antibiotics, which I assume the patient received, altered the pathology so much that the only residual actinomycosis was in the subphrenic space. The gross description — namely, a very productive inflammatory response with little central necrosis — best fits this diagnosis. Actinomycosis would account for a smoldering infection, low-grade fever and continued elevation of the white-cell count, with chronic systemic symptoms.

One other possibility I should like to mention is amebic abscess of the liver. An effort was made to rule out amebas in the stools, and there was no evidence that there was an intrahepatic abscess, so I would discard this diagnosis in favor of actinomycosis.

Dr. Thomas F. Paine, Jr.: Was any culture taken?

Dr. Edgar B. Taft: Yes. Direct culture on the blood-agar plate was negative. The thioglycollate medium grew colon bacilli and an alpha-hemolytic streptococcus.

Clinical Diagnosis

Subphrenic abscess.

Dr. J. Gordon Scannell's Diagnoses

Actinomycosis.
Subphrenic abscess.

Anatomical Diagnosis

Actinomycotic subphrenic abscess, with extension into liver.

Pathological Discussion

Dr. Taft: The diagnosis of actinomycosis was suggested by Dr. Richard H. Sweet in his first postoperative note; apparently he believed the character of the abscess suggested actinomycosis.

Dr. Helen S. Pittman: I think Dr. Sweet has suggested the diagnosis oftener than anyone else in the hospital.

Dr. Kane and I went over the cases of actinomycosis in this hospital a couple of years ago; this case points up what we found — that is, if the condition was considered, it was fairly easy to make the diagnosis, but as a rule it was not considered until about the third entry to the hospital.

Dr. Taft: The third operation was a re-exploration of the draining sinus and the subphrenic space, in which no pus was found. Dr. Sweet found a 5-cm. area of increased firmness in the liver and took a needle biopsy of this portion of the liver. The tissue removed from the wall of the sinus in the subphrenic space showed nothing but acute and chronic inflammation, with some necrosis and granulation tissue. The needle biopsy of the mass in the liver was composed of dense fibrous tissue infiltrated with moderate numbers of inflammatory

cells and a few colonies of bacillary organisms whose colonial form was quite characteristic of actinomycosis. These organisms were gram positive. However, the culture of this material has to date grown nothing but an anaerobic, gram-negative bacillus. The Department of Bacteriology tells me that in an occasional case diagnosed on section or on smear of infected material, no organism could be grown. We must assume, until something else is shown to be more likely, that this patient had actinomycosis.

DR. LEWIS KANE: I think the most accurate way to make such a diagnosis is examination of the sections and not bacteriologic culture.

CASE 39362

PRESENTATION OF CASE

First admission. A fifty-four-year-old former chef was admitted to the hospital because of chest pain.

The patient was well until eighteen months before admission, when he had a sudden severe pain in the chest lasting about three hours. He was taken to another hospital, where an electrocardiogram was said to have demonstrated a myocardial infarction. After eight weeks of inactivity he was free of symptoms and returned to work. He had no further difficulty until nine months before entry, when over a short time his ankles, legs and abdomen became markedly swollen. He was readmitted to the hospital, where he lost 42 pounds on a program of digitalis, Mercuhydrin and salt restriction. He was discharged on this program. While in the hospital he had an episode characterized by thick speech and weakness of the left arm and leg, all of which cleared after twenty-four hours. During the previous two weeks he had insomnia and orthopnea requiring two pillows for relief for the first time, as well as three episodes of paroxysmal nocturnal dyspnea. Two nights before admission he was awakened by a sharp pain in the right lower anterior part of the chest. This improved by morning, recurred the next night and again diminished by morning. The taking of a deep breath or pounding of the chest partially reduplicated the pain.

He did not have cough, sputum, hemoptysis, sweats or known fever. He had a history of a duodenal ulcer for fifteen years. In the other hospital the blood pressure was recorded as 130 systolic, 90 diastolic, and 170 systolic, 100 diastolic, on the two admissions.

Physical examination showed a man who appeared older than his stated age and chronically, but not acutely, ill. The neck veins were distended. The lungs were clear. The maximum impulse of the heart was in the anterior axillary line in the sixth interspace. The cardiac rhythm was regular; there were no murmurs; the aortic second sound equaled the pulmonic. The liver edge was percussed 3 cm. below the xiphoid; otherwise the abdomen was normal. There was +++ ankle edema.

The temperature was 100°F., the pulse 120, and the respirations 20. The blood pressure was 132 systolic, 88 diastolic.

A urine specimen had a specific gravity of 1.022, and gave a + test for albumin but was otherwise normal. The hemoglobin was 15 gm. and the white-cell count 16,600, with 87 per cent neutrophils.

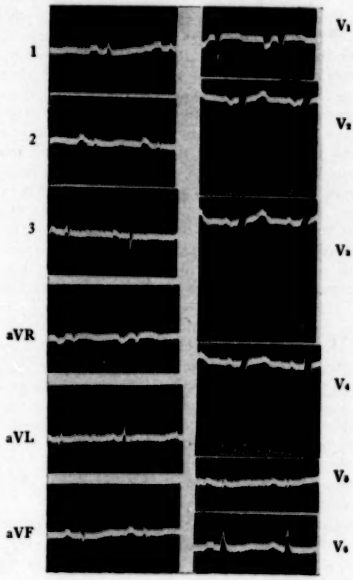

FIGURE 1.

The blood chemical determinations were normal. An electrocardiogram demonstrated a normal rhythm at a rate of 75, a PR interval of 0.20 second and a QRS interval of 0.08 second, with a normal axis. There was a tendency to low voltage. The T waves were flat or low and upright in Leads 1, 2, aVL, aVF, V_5 and V_6 and upright in Leads V_1, V_2, V_3 and V_4. The P waves were rather broad throughout (Fig. 1).

In the hospital the patient had a similar episode of chest pain of a pleuritic type.

A roentgenogram of the chest disclosed densities consistent with pulmonary infarcts, enlargement of the left ventricle and engorgement of the vessels of the lung roots (Fig. 2). In the lateral projection, the large left ventricle and the prominence of the left

atrium were shown against the barium-filled esophagus (Fig. 3). On the third hospital day a bilateral superficial femoral-vein ligation was performed. No thrombi were found in the femoral veins. The patient was treated with Dicumarol, but seven days later while on this therapy, he had another pulmonary infarct, again confirmed by x-ray examination. He gradually improved, the shadows in the lung cleared partially, and he was discharged after about a month in the hospital on a regimen of digitalis and a low-salt diet.

Second admission (about one month later). In the interval he had done fairly well. He had been receiving Mercuhydrin twice a week with decreasing

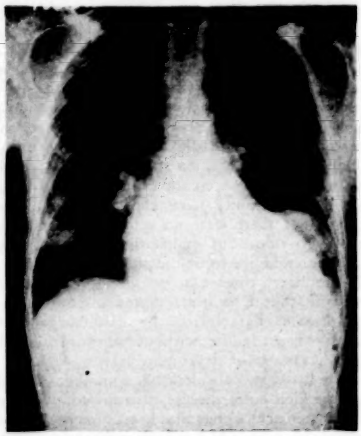

FIGURE 2. *Roentgenogram of the Chest Five Months before Death. Note the multiple pulmonary infarcts, the enlargement of the left ventricle and the engorgement of the vessels of the lung roots.*

effect. Dyspnea became worse. At the time of a visit to the Emergency Ward two days before the second admission, he complained of nausea and vomiting; and a gastrointestinal series revealed a gastric ulcer.

Physical examination showed the patient to be moderately dyspneic. Findings were the same as before except for the presence of a high-pitched, harsh, Grade 3, fairly sharply localized, apical systolic murmur. He was treated with bland diets and a cardiac regimen and discharged improved after three weeks.

Final admission (two and a half months later). In the interval he did fairly well. Three nights before admission, he began to feel dizzy. This persisted for several hours but was not associated with other symptoms. Two days before entry he had "the virus," characterized by fever, chilly sensations, nausea, vomiting and diarrhea, but these symptoms lasted only one day. On the morning of the day of admission while eating breakfast, he began to topple over, his face was drawn to the left, and his speech seemed thick for a few minutes. A physician found him to have a left hemiplegia and sent him to the hospital.

Physical examination revealed a confused man who was unable to follow commands very well but was not aphasic. The neck veins were distended 4 cm. above the clavicle at 40°. There were a few moist rales over the left lower lobe posteriorly. Cardiac findings were as before; the liver edge was felt two fingerbreadths below the right costal margin. Significant neurologic findings were a left homonymous field defect, paralysis of left lateral conjugate gaze, turning of the head to the left, left-sided hemi-

FIGURE 3. *Lateral Roentgenogram of the Chest Taken Three Weeks after That Shown in Figure 2. The large left ventricle and the prominence of the left atrium are shown against the barium-filled esophagus.*

plegia (face, arm and leg) and extensor plantar reflex on the left.

The temperature was 101.8°F., the pulse 100, and the respirations 30. The blood pressure was 130 systolic, 90 diastolic.

The urine gave a +++ test for albumin but was otherwise normal. The hemoglobin was 14.5 gm. per 100 cc., and the white-cell count, 15,000, with 82 per cent neutrophils, 12 per cent lymphocytes and 6 per cent monocytes. The blood chemical determi-

nations were normal. Cheyne–Stokes respirations developed, and the patient became comatose, with rising temperature, pulse and respirations, and died on the third hospital day.

Differential Diagnosis

Dr. Evan Calkins*: Since there are a great many different varieties of heart disease and only three main types of strokes I shall start at the end and work in the opposite direction, in the hope that I can establish a framework within which I can consider the fundamental type of heart disease and its relation to the episodes in the lung and brain. The final picture, with its sudden onset, is more consistent with hemorrhage or embolism than thrombosis; the fatal nature and large size of the lesion suggests hemorrhage; the facts that the patient had no stiff neck and was conscious, and particularly that he had a transient hemiplegia during the second admission to the outside hospital are much more suggestive of embolism. I think, therefore, that the final cerebral episode was an embolism, which, from the neurologic findings, was probably localized in the posterior ramifications of the right middle cerebral artery and probably involved a fairly large area. I should predict that this was a "red" infarction of large size, with hemorrhage occurring secondary to the infarction and accounting for the rapid death.

The patient had repeated episodes of chest pain, pleuritic in nature, not followed by hemoptysis but followed by the appearance of new shadows in the x-ray films of the lungs.

May I see those films?

Dr. Stanley M. Wyman: It will not be very hard to point out the x-ray findings in view of the explicit description of the protocol (Fig. 2). These densities lying out in the periphery — one is superimposed on the left hilus lying far anteriorly — are quite characteristic of infarction; they are homogeneous, and they lie against the major pleural surface. The second examination shows some increase in size of the shadows.

Dr. Calkins: During the first admission?

Dr. Wyman: Yes.

Dr. Calkins: The heart size seems to have increased.

Dr. Wyman: The heart is definitely abnormal. This film, taken still later, demonstrates a new lesion in the left lower lobe, and the lateral view shows a large infarction lying far posteriorly. The heart shadow is grossly enlarged. It is greatly enlarged in the region of the ventricles — I think chiefly the left ventricle. It is also enlarged posteriorly — high and just below the carina; this can be faintly seen through the central portion of the heart shadow; and I would take the enlargement to be of the left atrium.

Dr. Calkins: Conspicuously?

Dr. Wyman: Fairly so. If it were not for the huge left ventricle, you would be more impressed by it. The pulmonary vessels are not particularly enlarged on the later films, but they are fairly large on the admission films suggesting that the patient did have congestive heart failure. There was some fluid in the pleural spaces at that time.

Dr. Calkins: Do you have a film taken on the second admission? I am interested in whether the heart had enlarged during the course of this illness.

Dr. Wyman: The last films, taken about a month later, show the heart still greatly enlarged. This film shows particularly well the enlargement of the left atrium outlined by the barium-filled esophagus (Fig. 3).

Dr. Calkins: Unless I am wrong in assuming that the cerebral episode was an infarct, I am left with heart disease and embolic phenomena to both pulmonary and peripheral circulation. It is possible that this "virus infection" was a small mesenteric embolus, but it was minor and resolved quickly so I shall not bring that in in this manner. Any variety of heart disease may easily be associated with phlebothrombosis of the femoral veins, and the pulmonary emboli can come from this source. The facts that no clot was found and that the pulmonary infarcts developed after the ligation of the superficial femoral veins, even in the presence of Dicumarol, do not make that possibility particularly unlikely. Also, the fact that there were no symptoms in the legs whatsoever rules out phlebothrombosis. Nevertheless, I should like to tie the pulmonary infarcts in with the heart disease more directly within the framework that I have attempted to construct — heart disease characterized by cardiomegaly and congestive heart failure, without murmurs originally but with a murmur developing later.

I have listed for consideration a number of conditions in which heart disease is associated with embolic phenomena. Congenital heart disease may lead to mural thrombosis and embolism, but no murmurs were heard until late in the course, so that I doubt if the heart disease was of the congenital, valvular sort. The possibility, however, of defect of the interatrial or, less likely, interventricular septum, thus permitting paradoxical embolization from the femoral veins to the brain, is one that must be considered. The large P waves (Fig. 1) and the large atrium might go with an interatrial septal defect, but for a number of reasons I should rather not make that my primary diagnosis. The facts that the patient was not cyanotic, that no murmurs were heard until late and that there was no axis deviation in the electrocardiogram do not rule out congenital heart disease or a septal defect, but I should like to have more supporting evidence before making such a diagnosis.

Subacute bacterial endocarditis is suggested by heart disease with embolic phenomena, but there was no collateral evidence in the form of petechiae, splenomegaly, murmur or anemia.

*Assistant in medicine, Massachusetts General Hospital.

The possibility that the heart disease was secondary to the vascular disease, rather than vice versa, must be considered. Could the heart disease have been secondary to the infarcts? Perhaps the initial episode of chest pain was a pulmonary rather than a myocardial infarct. I do not think the picture was that of cor pulmonale, however, so I shall not consider that further. Polycythemia vera is intriguing because it would bring in the ulcer with the rest of the picture. Certainly, the hemoglobin was not striking, unless the patient was bleeding from the ulcer, and there was no evidence for this. Furthermore, I do not think it would have produced this type of heart disease.

DR. WYMAN: It was a real ulcer.

DR. CALKINS: I cannot dismiss that as readily as I had planned. Duodenal ulcers are the ones most likely to be associated with polycythemia rather than gastric ulcers.

Connective-tissue diseases come next. Rheumatic fever would certainly explain these two phenomena — the heart disease and the emboli. Nevertheless, there were no diastolic murmurs, and the systolic murmur was only heard terminally. I do not think this was rheumatic heart disease. The vascular phenomena, perhaps with the heart disease on that basis, may have been due to polyarteritis. I do not think this is very likely because the vessels involved in these infarcts were quite large ones and there was no collateral evidence for that disease. Certainly, one should think of lupus erythematosus with the Libman–Sacks type of picture, but there was no collateral evidence of that.

I skip over neoplastic heart disease; I suppose that one might encounter a carcinoma of the stomach that had metastasized to the heart with heart failure on the basis of cor pulmonale or on the basis of invasion of the heart muscle. I have heard of a patient seen here some time ago[1] who had a metastatic tumor of the heart with embolic phenomena, but I do not feel very happy about diagnosing it in this case.

Amyloidosis and sarcoidosis will produce heart disease without murmurs. Primary amyloid disease may involve the smooth musculature and also the vasculature — but there was nothing here to corroborate that. With nutritional heart disease, one thinks of a large heart with failure and no murmur. There is no reason to bring that in except in one regard. Subendocardial fibrosis has been thought by some physicians, particularly Smith and his coworkers,[2] to be associated with a vitamin deficiency, so there may be a relation.

I think this was either subendocardial fibrosis or the much more common coronary-artery disease. Subendocardial fibrosis would explain the embolic phenomena occurring at widely spread intervals better than coronary-artery disease, in which the embolic phenomena occur more in relation to an episode of acute myocardial infarction; subendocardial fibrosis would also explain the emboli to both pulmonary and peripheral circuits better than coronary-artery disease. One case discussed and diagnosed by Dr. Gordon S. Myers[3] two years ago presented much the same picture; it was also diagnosed as duodenal ulcer, but that was not borne out on pathological examination. The development of hypertension with the onset of failure can also occur with subendocardial fibrosis. Chest pain, true angina, is not part of subendocardial fibrosis, but the patients experience some substernal distress. I think the episodes described in the outside hospital would be a good point against subendocardial fibrosis.

All in all, however, subendocardial fibrosis is a rare condition. Coronary-artery disease, with diffuse scarring of the myocardium, perhaps with a major myocardial infarction and certainly with numerous small infarcts, with embolic phenomena to the brain secondary to the heart disease, and with embolic phenomena to the lungs either secondary to the heart disease or secondary to phlebothrombosis of the femoral vein are the diagnoses I should make if I saw the patient clinically and the ones I shall make at present. I shall choose one diagnosis and say that the emboli were secondary to the heart disease.

DR. JOHN T. QUINBY: Do you think this could have been mitral stenosis?

DR. CALKINS: No; I do not think so. I think the mitral stenosis would have been very queer to produce no murmur. In mitral stenosis there is usually much more dyspnea and left-sided failure early in the history. Here it developed after the right-sided failure was already well established.

DR. WALTER BAUER: How are you going to explain the large left atrium?

DR. CALKINS: Mitral stenosis would, of course, bring in the large left atrium, as would congenital heart disease. The subendocardial fibrosis would explain that point better than coronary-artery disease because that process might involve the atrium. Nevertheless, as I went over the story before seeing the x-ray films, I must say I was fairly happy with my diagnosis and I think I shall stick with it.

DR. RICHARD J. CLARK: With the appearance of the systolic murmur perhaps an increasing size and dilatation of the heart was developing. Cannot the enlarged left atrium be explained on the basis of a relative mitral regurgitation with a failing heart rather than implying a diagnosis of rheumatic valvular disease?

DR. WYMAN: To me this looks like a fairly straightforward case of rheumatic heart disease with a large atrium and a large ventricle, either left or right or both. I should be surprised if it was not that.

DR. CALKINS: Certainly, rheumatic heart disease would account for the heart disease and for the

embolic phenomena, but I agree with Dr. Clark that the murmur appeared rather late in the course.

DR. BENJAMIN CASTLEMAN: There was no arrhythmia, which one would like to have in a rheumatic heart associated with embolic phenomena.

DR. CLARK: The large P waves in the electrocardiogram certainly can be explained on the basis of pulmonary infarction without the implication of disease of the mitral valve.

DR. WYMAN: What was the PR interval?

DR. CLARK: It was the top limit of normal for that age.

CLINICAL DIAGNOSIS

Coronary-artery disease, with old myocardial infarction and embolus to right middle cerebral artery.

DR. EVAN CALKINS' DIAGNOSIS

Coronary-artery heart disease, with emboli to lungs and brain.

ANATOMICAL DIAGNOSES

Coronary-artery disease, with old and recent myocardial infarctions of both ventricles.

Mural thrombi, both ventricles.

Cerebral and pulmonary embolism and infarction.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The cause of this man's death, as Dr. Calkins stated, was a massive infarction of the right hemisphere — frontoparietotemporal; it was anemic rather than hemorrhagic. The embolus occurred at the bifurcation of the right internal carotid artery, a vessel that showed no arteriosclerosis at all, so that I think there is no question that this was an embolus rather than thrombus. There were, as was obvious from the x-ray films, multiple infarcts in both lungs; both lower lobes were massively infarcted and the lingula of the left upper lobe was also infarcted. The right middle lobe was free from infarction. The cause of the embolic phenomena was in the heart. Almost the entire left ventricle was massively infarcted and contained a huge mural thrombus that was quite organized, and yellowish with layer after layer of thrombus — apparently this was part of the infarction that the patient had a year and a half before admission. He must have had more infarction superimposed because we found other areas that were fresher than the old infarction and also a great deal of fresh thrombosis superimposed on this old mural thrombosis. This infarct involved a large portion of the septum and extended through the septum to the right ventricle, producing mural thrombi, which were the source of the emboli to the lungs. The leg veins did not contain thrombi. The heart, as Dr. Clark mentioned, was dilated, which perhaps accounts for the enlarged left atrium. There was no valvular disease anywhere. The coronary arteries were extremely sclerotic, with multiple occlusions, some old and a few quite recent. I wonder whether Dr. Clark would comment on the electrocardiogram.

DR. CLARK: The interesting thing regarding the electrocardiogram is that there was an R wave that persisted across the chest; there was no absent R wave as one might have expected with a massive infarction involving the septum. This is a strikingly innocuous-looking tracing for a massive septal infarct but we are not at all certain about the time relation (Fig. 1).

DR. CASTLEMAN: I think the patient had the massive infarction eighteen months before admission and that the mural thrombosis was being built up during that time on the old as well as on the more recent infarctions.

DR. CALKINS: Do you think the episode of chest pain that developed six months before admission might have been caused by another infarct?

DR. CASTLEMAN: Yes; but there was so much infarction it is hard to tell when each occurred.

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ANERGY IN TUBERCULOUS PATIENTS

THE significance of the tuberculin test in patients with active or latent tuberculosis has received considerable study in the past, and interest in this subject has been revived since the advent of highly effective therapy. Among other things it has been well known that the failure of patients with active tuberculosis to give a typical reaction to tuberculin is associated with a poor prognosis. A number of observations on various aspects of this subject have been made over the past few years by Woodruff and his co-workers at the William M. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium). In some of their earlier studies, these authors were able to show that in far-advanced tuberculosis untreated with streptomycin, the degree of tuberculin sensitivity — as roughly estimated by the greatest dilution of tuberculin required to elicit a reaction and the size and intensity of that reaction —declines rapidly during the last few weeks of life.[1,2]

When streptomycin was first introduced, Feldman, Hinshaw and Mann[3] carried out experiments indicating that tuberculous infection of guinea pigs could be controlled so completely that a large proportion of the animals treated with streptomycin became tuberculin negative. During the first two years after the introduction of streptomycin, observations made before and after treatment in 146 patients at the Maybury Sanatorium showed no marked change in tuberculin sensitivity at the conclusion of either six weeks or ninety days of streptomycin therapy. This has been the general experience with courses of therapy of similar duration, which are now considered to be brief and perhaps inadequate for many patients.

Recently, studies have been carried out in patients in whom treatment was begun when they were so critically ill as to have a low level of sensitivity to tuberculin. In most of these anergic or partially anergic tuberculous patients, the change in sensitivity that followed streptomycin therapy has been dramatic. The course of the cutaneous hypersensitivity of 36 such patients was followed by Woodruff and his associates[4] during treatment with streptomycin (with or without para-aminosalicylic acid); in every patient who responded favorably to antimicrobial therapy, the cutaneous hypersensitivity to tuberculin increased. Moreover, the increased tuberculin hypersensitivity of such patients frequently preceded roentgenographic evidence of improvement.

More detailed analysis was made of the prognostic significance of the changes in the tuberculin reaction resulting from effective therapy.[5] The survival time of 169 anergic or partially anergic tuberculous patients was studied; 63 of these patients were treated for various lengths of time with streptomycin (alone or with PAS). At the end of a hundred and twenty days 72 per cent of those who received the chemotherapy were alive, and 51 per cent were still alive after three years. This is in sharp contrast to the results in the 106 patients who did not receive anti-

microbial therapy, only 9.5 per cent of whom survived for a hundred and twenty days and all of whom were dead at the end of three years. This is a remarkable demonstration of the effectiveness of chemotherapy even in such critically ill patients; it indicates that no case of active tuberculosis should be considered hopeless without an adequate trial of chemotherapy.

The current results of prolonged therapy of tuberculosis with regimens involving combinations of streptomycin with PAS or isoniazid, or both, have again raised the question whether true cures of tuberculosis may not be obtained in some cases. The question is particularly applicable to patients who have no demonstrable lesions after treatment and, perhaps even more so, to patients who have been subjected to resections of residual pulmonary lesions that have failed to yield demonstrable tubercle bacilli — or when tubercle bacilli can be seen in stained smears or sections but cannot be cultivated and do not produce infection in susceptible animals. Observations on the tuberculin reaction of these patients during prolonged follow-up periods after such treatment are urgently needed to help answer this important question.

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NEW ENGLAND REGIONAL COMPACT FOR HIGHER EDUCATION

Last year a recess commission reported in favor of the establishment of a new medical and dental school in Boston under state auspices.[1] There was evidence, both external and internal, that the report was conceived in haste. However, the recommendation, with the strong backing of Governor Dever, was favorably acted upon by the Massachusetts House of Representatives and failed of passage in the Senate by only two votes. After the change of regime on Beacon Hill, which cost some of the most ardent proponents of the new school their seats, the Commission took a new look at the problem; it is now exploring another and less radical solution.

A second report, published in June, considers the possibility of interstate co-operation in higher education among the six New England States, with particular reference to medical and dental training.[2] The report cites the plan for regional co-operation in higher education officially endorsed by the Southern Governors' Conference in 1948:

> Under the plan the South seeks to pool the established facilities of fourteen Southern States in order that the institutions within each State might better serve the entire region.
>
> First applied in the fields of medicine, dentistry and veterinary medicine, all of them high-cost fields, the plan provides that a State without facilities in these fields may pay the cost of educating its students at established public and private schools in other States of the region. For example, a State with no medical school within its borders may choose to avoid the costly and difficult task of creating new medical training facilities. Rather, the State Legislature may appropriate money for the education of a group of its medical students at colleges elsewhere in the region. It then enters into a contractual arrangement with the Board. The State agrees to pay a specified amount for the medical education of each of its students who are placed through the program. Medical schools located in the region also enter into agreements with the Board. They agree to provide openings for specified numbers of students, in return for which they receive a stipulated amount each year for the education of each student. At the present writing the States pay $1,500 per place per year for medical or dental training.
>
> The student pays resident tuition at the institution he attends. The institution retains full authority over the final acceptance of students and over the educational content of the program. Thus each participating State maintains a "medical school away from home."

The compact program in the South has been highly successful. More recently, Colorado, Montana, New Mexico, Oregon, Utah, Arizona, Idaho and Wyoming have entered into a similar agreement establishing a Western Interstate Commission for Higher Education.

The central purpose of these regional compacts is to provide specialized educational opportunities within the region, at cost, by strengthening and expanding existing facilities rather than by duplicating them. The Commission is well advised in weighing the costs and advantages to Massachusetts of participation in a New England regional compact as against those of setting up and operating its own medical and dental school.

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THE *FACTBOOK*

JUST published by the American Medical Association is a small booklet, *Factbook on Medical Education*, based on the data for the academic year 1951-52. It has been compiled to provide a source of quick reference to the enrollments, financial support and faculties of the medical schools of the country.

This country now has 72 medical schools and 7 basic-science schools with a total attendance of 27,076 students, the largest number ever enrolled. Compared with the figures of 1940-41 this is an increase of 26 per cent. Much has been said concerning the shortage of doctors but the fact remains that the population increased only 16.4 per cent in ten years whereas medical-school enrollments increased 22.8 per cent. In 1952, 6080 students received their degrees from medical schools, the largest class ever to graduate. Of the 79 medical and basic-science schools 41 are privately owned, 35 are state owned, and 3 are municipally owned. Two new schools have just admitted a freshman class in the last two years, and 4 state universities are expanding their basic-science schools to four-year medical schools. A new medical school has been started in New York, and the possibility of new medical institutions is being considered in three other states.

Operating expenses of these schools amount to $80,000,000, and almost $40,000,000 more has been spent for special teaching, research and miscellaneous expenses. Only 21 per cent of the operating budget comes from tuition fees. Of the 13,897 physicians on the teaching staffs, 49 per cent receive no income from their teaching, and only 20 per cent receive all their income from this source.

Many of the items in the *Factbook* should help answer the questions that every physician receives concerning the shortage of physicians and the efforts being made to obtain more doctors. More factbooks of a similar type about other phases of medicine would be of value.

RETIREMENT OF DR. WILINSKY

THE retirement on September 1 of Dr. Charles F. Wilinsky as director of the Beth Israel Hospital of Boston is an event of more than passing moment in public-health and medical administration. For Dr. Wilinsky, who has given only the last twenty-five years of his useful life to hospital administration, is a person whose lifelong dedication to public service has made him one of the very distinguished physicians of his day.

A past president of the American Public Health Association, recipient of an honorary master's degree from Harvard in 1941 and of the Lemuel Shattuck Award of the Massachusetts Public Health Association this year, he was best known, before he became director of the Beth Israel Hospital, as the organizer and director of Boston's health centers.

The *Journal* wishes Dr. Wilinsky a long and happy retirement with the expectation that its fruits will be abundant as well as mature.

Dr. Tobert de Lamballe, a distinguished physician of Paris, announces that a shock of electricity given to a patient dying from the effects of chloroform, immediately counteracts its influence, and returns the sufferer to life.

Boston M. & S. J., *September 7, 1853*

MASSACHUSETTS MEDICAL SOCIETY

REPORT OF MASSACHUSETTS DELEGATES TO AMERICAN MEDICAL ASSOCIATION

The following is the report of the Massachusetts delegates to the American Medical Association:

The House of Delegates of the American Medical Association, in session June 1 through 5 during the 102nd Annual Meeting of the A.M.A. in New York City, took important policy actions on veterans' medical care, medical ethics, osteopathy, intern training and a wide variety of subjects ranging from medical education to public relations. Highlights of the opening day session of the House were addresses by Dr. Louis H. Bauer, who delivered his term-end report as retiring president; and Mrs. Oveta Culp Hobby, United States Secretary of Health, Education and Welfare, and selection of Dr. Alfred Blalock as winner of the 1953 Distinguished Service Award.

The House also named Dr. Walter B. Martin of Norfolk, Virginia, as president-elect of the American Medical Association for the coming year. Dr. Martin will become president at the June, 1954 meeting in San Francisco, succeeding Dr. Edward J. McCormick of Toledo, Ohio.

The New York meeting was the largest ever held in the history of the American Medical Association, with the final figure of 17,958 physicians attending.

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The House gave approval to a recommendation from its Reference Committee on Insurance and Medical Service, submitted as a substitute for eight different resolutions concerning the treatment of non-service-connected disabilities by the Veterans Administration. In taking this action, the House reaffirmed and adopted the following recommendation originally presented at

the Denver Meeting last December by the Special Committee on Federal Medical Services:

> Your Committee recommends with respect to the provision of medical care and hospitalization benefits for veterans in Veterans Administration and other federal hospitals that new legislation be enacted limiting such care to the following two categories:
>
> (a) Veterans with peacetime or wartime service whose disabilities or diseases are service-incurred or aggravated, and
>
> (b) Within the limits of existing facilities to veterans with wartime service suffering from tuberculosis or psychiatric or neurological disorders of non-service connected origin, who are unable to defray the expenses of necessary hospitalization.
>
> Your Committee recommends that the provision of medical care and hospitalization in Veterans Administration hospitals for the remaining groups of veterans with non-service connected disabilities be discontinued and that the responsibility for the care of such veterans revert to the individual and the community, where it rightfully belongs.
>
> It is the belief of your committee that the medical profession must concern itself, not with the numbers of "chiselers" in Veterans Administration hospitals nor with the efficacy of the Veterans Administration in the administration of enabling legislation, but rather with the broad question of whether such legislation is sound, whether the federal government should continue to engage in a gigantic medical care program in competition with private medical institutions and whether the ever-increasing cost of such a program is a proper burden to impose on the taxpayers of the country. A consideration of this problem must of course be predicated upon a concern for the health of the entire population and not just a particular segment.

This courageous action of the House was taken in spite of the active opposition of the American Legion and representatives of the Veterans Administration. Great credit for this must be given to Dr. Harrison Shoulders of Tennessee who for 20 years had warned the House of Delegates of the effects on the voluntary hospital system of the spread of the V.A. care of non-service connected disabilities.

•••

Eleven resolutions dealing with publicity regarding unethical conduct of physicians were brought before the House as a result of recent newspaper and magazine articles reporting statements attributed to Dr. Paul R. Hawley. The House adopted a committee report which recommended no action on the eleven resolutions but which reaffirmed the supremacy of the A.M.A. code of ethics and urged that the Judicial Council study suggested revisions concerning methods of billing.

"The Principles of Medical Ethics as formulated, interpreted, and applied by the American Medical Association must be considered the only fundamental and controlling application of ethics for the entire profession," the reference committee report said. "Any statement relating to ethical matters by other organizations within the general profession of medicine advances views of only a particular group and is without official sanction of the entire profession as represented by the American Medical Association."

Condemning generalized statements regarding the ethics of physicians, the report went on to say:

> Your reference committee believes that the harm done to the public and to the profession by the current articles which lower the confidence patients have in their doctors cannot be objectively evaluated. This highlights the fact that, when individuals or groups without official status in the American Medical Association utter or publish ill-considered statements, the result too often is that the confidence of the public in the medical profession is placed in jeopardy.
>
> The reference committee believes that the members of the House of Delegates have demonstrated their devotion over the years to the principles of American democracy. This devotion includes the right of free speech.

The report also urged that the American Medical Association continue to inform its members and the public of its stand on matters pertaining to abuses and evils in the practice of medicine.

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The most controversial issue brought before the House at the New York meeting proved to be the question of immediate or deferred action on the report of the Committee for the Study of Relations Between Osteopathy and Medicine. The House, after two hours of vigorous, spirited debate, adopted the majority report of the Reference Committee on Miscellaneous Business, thereby postponing action until the June, 1954, meeting and allowing further study by the delegates and the state associations.

The recommendations of the Committee for the Study of Relations Between Osteopathy and Medicine were as follows:

1. That the House of Delegates declare that so little of the original concept of osteopathy remains that it does not classify medicine as currently taught in schools of osteopathy as the teaching of "cultist" healing.
2. That the House of Delegates state that pursuant to the objectives and responsibilities of the American Medical Association which are to improve the health and medical care of the American people, it is the policy of the Association to encourage improvement in the undergraduate and postgraduate education of doctors of osteopathy.
3. That the House of Delegates declare that the relationship of doctors of medicine to doctors of osteopathy is a matter for determination by the state medical associations of the several states and that the state associations be requested to accept this responsibility.
4. That the Committee for the Study of Relations Between Osteopathy and Medicine or a similar committee be established as a continuing body.

A minority report of the reference committee urged approval and adoption of those recommendations at the New York meeting. The majority report, which ultimately won out, included the following recommendations by the Board of Trustees:

> Because of the length of the report and the controversial nature of the subject, the Board feels that the House should have adequate time for its study and that the state associations should have opportunity to express their opinions.
>
> Therefore, it is recommended that the Committee be continued but that action on the report be deferred until the June, 1954 session. It is suggested that at that time the House be prepared to answer the following questions:
>
> 1. Should modern osteopathy be classified as "cultist" healing?
> 2. Since the objectives of the American Medical Association include improvement in undergraduate and postgraduate education, should doctors of medicine teach in osteopathic schools?
> 3. Should the relationship of doctors of medicine to doctors of osteopathy be a matter for determination by the several state associations?

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Five resolutions came before the House with regard to the Essentials of an Approved Internship, which were adopted at the December, 1952 meeting. The Reference Committee on Medical Education and Hospitals recommended a substitute resolution which was adopted by the House after considerable discussion. The action abolishes the rule whereby approval may be withdrawn from an internship program which for two consecutive years fails to obtain at least two-thirds of its slated complement of interns. The resolution also calls for further study of the Essentials by a committee appointed by the Speaker of the House, at least half of whom are doctors in private practice not connected with medical schools or affiliated hospitals.

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Among the many other actions taken, the House reaffirmed its endorsement of the principles embodied in Senate Joint Resolution No. 1 concerning international treaties or agreements which interfere with domestic laws or rights.

Dr. Elmer Henderson addressed the House on the achievements of the American Medical Education Foundation. A total of $1,687,501.00 was given to the nation's 79 medical schools during 1952. About half was contributed by industry and half by the medical profession. Dr. Harlan English introduced a resolution that the various states follow the Illinois plan of adding $20.00 per year to members' dues for the Medical Foundation. In what proved to be his last appearance before the House, Dr. Frank Lahey revealed his deep interest and work for the Foundation; he said: "We are making headway in interesting industry in the roughly 10 million dollars a year deficit the medical schools run."

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Massachusetts Delegates and other interested members attended all sessions and took an active part in the proceedings. Dr. Lawrence Dame served as teller, Dr. Charles Hayden served on

the Reference Committee on Industrial Health. Dr. Earle M. Chapman served on the Reference Committee on Hygiene and Public Health. Dr. Patrick Sullivan was defeated for the office of Vice President by a narrow majority of votes for Dr. Carl H. Gellenthien of New Mexico.

Dr. Charles Hayden of Massachusetts presented the following:

Resolved, That the Speaker of the House of Delegates be, and is hereby, directed to appoint a representative committee to study and report as soon as possible on the feasibility of establishing a Department of Health to include the following functions, facilities, and personnel as recommended by the Commission on the Organization of the Executive Branch of the Government (Hoover commission):

(A) The general hospitals of the Armed Forces in the continental United States (except a medical center for each of the three services) and station hospitals (certain of which the Navy calls "dispensaries") in the continental United States except those at outlying posts so located that other hospitals of the Department of Health would not be near enough to provide the care required.

(B) The hospital functions of the Veterans' Administration in toto, including the outpatient services in the field offices of the Veterans' Administration.

(C) The four nonmilitary hospitals in the Canal Zone.

(D) The hospitals of the Public Health Service.

(E) The functions, facilities, and personnel of the Public Health Service.

Dr. George S. Klump, Chairman of the Reference Committee on Legislation and Public Relations, submitted the following report, which was adopted:

Your Reference Committee studied the resolution presented by Dr. Hayden of Massachusetts on the subject of creation of a Department of Health. Your reference committee reaffirms the stand of the House that it is the continuing policy of the American Medical Association to strive for the creation of a federal Department of Health. Now working on this problem is a subcommittee of the Council on Medical Service known as the Committee on Federal Medical Services which is charged with the responsibility of studying all activities in this field. It is the opinion of your reference committee that no useful purpose could be gained by the creation of a separate committee as recommended in the resolution, as this would duplicate the function and activities of the current committee. The reference committee is of the opinion that the subcommittee of the Council should be asked to study the various points outlined in this resolution.

EARLE M. CHAPMAN, M.D.

BOSTON MEDICAL LIBRARY

LUCIFER SMILING

Lucifer, Lord Chief Justice under Beelzebub
Master of all the damned who stormed the sky.
Are ye risen again in this place in the Hub
And has your eternal damnation now gone awry?

The Cabots and Abbots and Babots and Lodges
Might not soberly wonder or even surmise
That the fallen possess the wiliest dodges
And may rise again slowly — if not to the skies.

No pale Athene, or perch for raven or rooks,
Lucifer thou are housed most surely here.
Damnation among ten thousand ancient books
Is no damnation with no damnation near.

Lucifer, fallen angel, now bibliophile,
Surely your infernal master Beelzebub
Would read profoundest wisdom in your devil's smile
Should he visit you here at 8 Fenway, the Hub.

F. E. I.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Biochemistry of Gastric Acid Secretion. By Edward J. Conway, M.D., D.Sc., F.R.S., professor of biochemistry and pharmacology, University College, Dublin, Ireland. 8°, cloth, 185 pp., with 29 illustrations and 13 tables. Springfield, Illinois: Charles C Thomas, 1952. $6.50. (Publication No. 119, *American Lecture Series.*)

This monograph discusses the various aspects of gastric acid secretion, including the role of the hydrogen ions, the "Redox" theory, energetics, neutralization and gastric urease. There is a bibliography of 12 pages and a good index. The small book should be in gastrointestinal and biochemical collections.

Practical Blood Grouping Methods: A manual of immunohematology. By Robert L. Wall, M.D., Department of Research Medicine, Ohio State University Hospital, Columbus, Ohio. 8°, cloth, 175 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.00. (Publication No. 122, *American Lecture Series.*)

This manual furnishes information on the various blood groups and on immunohematology in general. The literature of the subject is reviewed and evaluated, and there is a bibliography of 145 references.

Dermatology: Essentials of diagnosis and treatment. By Marion B. Sulzberger, M.D., professor and chairman, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, director of dermatology and syphilology, Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center, and consultant dermatologist to the Bureau of Medicine and Surgery, United States Navy; and Jack Wolf, M.D., associate professor of clinical dermatology and syphilology, New York University Post-Graduate Medical School, attending dermatologist and syphilologist, Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center. 8°, cloth, 592 pp., with 65 illustrations, 18 tables and 8 colored plates. Chicago: Year Book Publishers, Incorporated, 1952. $10.00.

This fourth edition of a standard book has been completely revised. The publishing is good, except that a lighter nonglare paper could have been used with distinct advantage to readers.

Leitfaden der Neurologie. By Prof. Dr. Med. F. Laubenthal, physician-in-chief, Psychiatrischen und Nervenklinik der Städtischen Krankenanstalten Essen; A. Pl. Professor, Universität Bonn. Fifth revised edition. 8°, cloth, 291 pp., with 88 illustrations. Stuttgart: Georg Thieme, 1953. DM 28. — (Distributed by Grune and Stratton, New York.)

This textbook on clinical neurology, now in its fifth edition, has been revised and brought up to date. The whole of the nervous system is covered, and an appendix consists of a table of muscles, their functions and the paralyses affecting them. There is a good index, and the publishing is excellent.

Practical Clinical Chemistry: A guide for technicians. By Alma Hiller, Ph.D., associate attending biochemist in charge of clinical chemistry, Presbyterian Hospital of the City of Chicago, and associate professor of biological chemistry, University of Illinois College of Medicine. 8°, cloth, 266 pp., with tables. Springfield, Illinois: Charles C Thomas, 1953. $6.50.

The procedures in this guide have been chosen as representative analyses commonly used in a hospital laboratory. The preliminary chapters, which deal with general procedures, standard solutions of acid and alkali and photometry, are followed by chapters on the various methods for determination of substances arranged alphabetically from amylase to uric acid. The outlines are printed twice in the text — those in the back of the volume in perforated form, for removal for reference use. There is a good index. The book should prove useful to technicians.

The Pharmacology of Anesthetic Drugs: A syllabus for students and clinicians. By John Adriani, M.D., director, Department of Anesthesiology, Charity Hospital, New Orleans, Louisiana, professor of surgery, Tulane University of Louisiana School of Medicine, and associate clinical professor of surgery, Louisiana State University School of Medicine. Third edition. 4°, cloth, 179 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $9.50.

The essential value of this book is shown by the need of five printings of the second edition, first published in 1941, one year after the first edition was issued. This new edition has been completely revised, and the text brought up to date, resulting in a larger volume. A glossary of terms and a bibliography conclude the text. There is an extensive index. The book should be in all collections on anesthesia.

Biochemistry of Disease. By M. Bodansky and O. Bodansky. Thoroughly revised and enlarged by Oscar Bodansky, M.D., Ph.D., professor of biochemistry, Sloan Kettering Division, Cornell University, Medical College, attending clinical biochemist and chief, clinical biochemistry, Memorial Center for Cancer and Allied Diseases, and lecturer on pediatrics, New York University Post-Graduate Medical School. Second edition. 8°, cloth, 1208 pp., with 71 illustrations and 160 tables. New York: Macmillan Company, 1952. $12.00.

The author, in this new edition of a book first published in 1952, has completely revised his text. Substantial lists of references have been appended to each chapter. An appendix on the normal clinical biochemical values has been added. There is a good index, and the publishing is excellent.

Medicina Fennica, XXIII, 1951. Edidit Suomalainen Lääkäriseura Duodecim, Tauno Putkonen, M.D., M.P.H., Antti Telkkä, M.D. 8°, paper, 127 pp. Helsinki: Medicina Fennica, 1952.

This serial publication lists the important medical articles published in Finland during 1951. The material is arranged alphabetically by subject, and there is an index of authors.

Die gesunde und die kranke Wirbelsäule in Röntgenbild und Klinik: Pathologisch-anatomische Untersuchungen. By Geh. Med.-Rat Prof. Dr. med. et Dr. med. vet. h. c. Georg Schmorl (1932). Adapted for roentgenologic and clinical use by Prof. Dr. med. habil. Herbert Junghanns, Oldenburg (Oldb.). Third revised edition. 4°, cloth, 304 pp., with 403 illustrations. Stuttgart: Georg Thieme, 1953. DM 72. (Distributed by Grune and Stratton, New York.)

Dr. Junghanns, in this combined atlas and text, discusses the spine in health and in various diseases. The first edition was written by the late Dr. Schmorl in 1932, the second by Dr. Junghanns in 1951. The illustrations and the publishing are excellent. There is a comprehensive bibliography of 34 large quarto pages and a good index.

Citomorfologia e funzione del plasmocita. By Dr. Renato Curletto. 8°, paper, 126 pp., with 32 illustrations. Pisa: Edizioni Omnia Medica, 1953. L.1200.

Dr. Curletto discusses the plasmocite, including its constant and inconstant characteristics, its nuclear aspect and its activity and function. There are 4 plates of illustrations and a bibliography.

The Literature on Streptomycin, 1944–1952. By Selman A. Waksman. 8°, cloth, 553 pp. New Brunswick, New Jersey: Rutgers University Press, 1952. $5.00.

This second edition of an important bibliography has been revised and brought up to date. The total references now number 5550. There are extensive indexes of authors and subjects. The book is well published and is recommended as an essential reference tool for all medical libraries.

Pamiętnik XXXV Zjazdu Chirurgów Polskich. XIX Zjazdu towarzystwa chirurgow polskich W Lublinie, 5, 6 i 7. IV. 1951. R. ku czci Ludwika Rydygiera. 8°, paper, 562 pp. Warsaw: Panstwowy Zaklad Wydawnictw Lekarskich, 1952.

This volume constitutes the proceedings of the 35th Polish surgical congress, held at Lublin in 1951.

Die Röntgenuntersuchung der Harnorgane. By Dr. med. O. Kneise, a.o. professor of urology, Martin-Luther-Universität, Halle-Wittenberg; and Dr. Med. K. L. Schober, specialist in urology, Chirurgische Universitäts-Klinik, Halle (Saale). Fourth revised edition. 4°, cloth, 280 pp., with 323 partly colored illustrations. Leipzig: Georg Thieme, 1953. DM 32.

This standard atlas has been long out of print since the publication of the third edition in 1944. In this new edition it has been revised and brought up to date. The rontgenograms depict conditions of the various urinary organs, including the prostate. There is a chapter on tuberculosis. It is an excellent atlas.

Diseases of the Skin: A manual for students and practitioners. First compiled by the late Robert W. MacKenna, M.A., M.D., Ch.B. (Edin.). By Robert M. B. MacKenna, M.A., M.D. (Camb.), F.R.C.P. (Lond.), physician-in-charge, Dermatological Department, and lecturer in dermatology, St. Bartholomew's Hospital and Medical College, London, and physician to St. John's Hospital for Diseases of the Skin, London. With a chapter concerning radiology by I. G. Williams, F.R.C.S. (Eng.), D.M.R.E. (Camb.), F.R.R. (Gt.B.), director, Department of Radiotherapy, St. Bartholomew's Hospital, London, and consulting radiotherapist, Hospital for Sick Children, Great Ormond Street, London. Fifth edition. 8°, cloth, 611 pp., with 215 illustrations and 27 color plates. London: Baillière, Tindall and Cox, 1952. $8.00. (Distributed by William and Wilkins, Baltimore, Maryland.)

This standard English textbook, written primarily for the medical student and the general practitioner, and first published in 1927, has been revised and brought up to date. There are 27 color plates and a good index; the publishing is excellent.

Das Ulkus des Magens und Zwölffingerdarms als Problem eines Schutzstoffmangels. By Dr. H. Ramb, physician-in-chief, Surgical Division, Laurentius-Hospital Essen-Steele. 8°, paper, 68 pp., with 28 illustrations. Stuttgart: Georg Thieme, 1953. DM 6.50. (Distributed by Grune and Stratton, New York.)

Dr. Ramb discusses ulcers of the stomach and duodenum and the problem of their causation.

Technik der Blutgruppen- und Blutfaktoren-Bestimmung. By Dr. med. habil. Peter Dahr, Professor, Universität Göttingen, and head, Institut für Blutgruppenforschung Göttingen. Sixth revised edition. 8°, cloth, 320 pp., with 27 illustrations. Stuttgart: Georg Thieme, 1953. DM 24. (Distributed by Grune and Stratton, New York.)

Dr. Dahr has revised this new edition of his manual on the blood groups and their determination. The coverage is comprehensive in scope, and there is a bibliography.

Functional Endocrinology from Birth through Adolescence. By Nathan B. Talbot, M.D., associate professor of pediatrics, Harvard Medical School, and physician, Children's Medical Service, Massachusetts General Hospital; Edna H. Sobel, M.D., instructor in pediatrics, University of Cincinnati College of Medicine, and research associate, Children's Hospital Research Foundation and The Fels Research Institute, Antioch College; Janet W. McArthur, M.D., instructor in gynecology, Harvard Medical School, and assistant physician, Massachusetts General Hospital; and John D. Crawford, M.D., instructor in pediatrics, Harvard Medical School, and assistant physician, Children's Medical Service, Massachusetts General Hospital. 4°, cloth, 638 pp., with 218 illustrations and 59 tables. Cambridge: Harvard University Press, 1952. $10.00. (A Commonwealth Fund book.)

This new book considers all the glands now known to be organs of internal secretion, omitting the pineal body and the thymus, once believed to be in this class. The book has been written for those who seek practical information concerning the actions of endocrine systems in health and in ordinary disease, and the management of endocrinopathies as they occur in young people. The thyroid and parathyroid glands, the adrenal cortexes and medullae, ovaries, testes, anterior and posterior pituitary gland and pancreatic islets are discussed in detail. Lists of references are appended to the chapters. There is an extensive index, and the publishing is excellent. The book should be in all medical libraries and available to all persons interested in endocrinology and to pediatricians.

Clinical Obstetrics. By members of the staff of the Pennsylvania Hospital. Edited by Clifford B. Lull, M.D., and Robert A. Kimbrough, M.D., director, Division of Obstetrics and Gynecology, Pennsylvania Hospital, professor of gynecology and obstetrics, Graduate School of Medicine, University of Pennsylvania, and gynecologist, Graduate Hospital. 4°, cloth, 732 pp., with 392 illustrations and 8 color plates. Philadelphia: J. B. Lippincott Company, 1953. $10.00.

This composite book, which is the joint product of 20 specialists in their particular fields, is a record of practice of the Division of Obstetrics and Gynecology of the Pennsylvania Hospital and is intended for the student and general practitioner. The text is divided into nine sections, as follows: the anatomy and physiology of reproduction, normal pregnancy and the complications of pregnancy, normal and abnormal labor and operative obstetrics, the puerperal period, the newborn, maternal and neonatal mortality, nursing and legal aspects. Short lists of references are appended to the various chapters, and there is a good index. The illustrations and the publishing are excellent. The book should be in collections on the subject and should be of value to the general practitioner.

An Atlas of Skull Roentgenograms. By Bernard S. Epstein, M.D., associate radiologist, Jewish Hospital of Brooklyn, Brooklyn, New York; and Leo M. Davidoff, M.D., neurosurgeon, Mount Sinai Hospital, and director of neurologic surgery, Beth Israel Hospital, New York City. 4°, cloth, 415 pp., with 603 illustrations. Philadelphia: Lea and Febiger, 1953. $15.00.

This new atlas of the skull presents in order the normal skull, congenital conditions, trauma, infections and brain tumors in general, with five chapters on special types of tumors of the brain and skull. The illustrations are excellent, and there is a good index. The book should be in collections on radiology and neurology.

Lumbar Disc Lesions: Pathogenesis and treatment of low back pain and sciatica. By J. R. Armstrong, M.D., M.Ch., F.R.C.S., orthopedic surgeon to the Metropolitan Hospital, orthopedic surgeon to Lambeth Hospital and visiting orthopedic surgeon to Manor House Hospital (Industrial Orthopaedic Society). With a foreword by H. Osmond-Clarke, C.B.E., F.R.C.S., orthopedic surgeon, London Hospital, senior visiting surgeon, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, and civilian consultant in orthopedic surgery to the Royal Air Force. 8°, cloth, 288 pp., with 56 illustrations, 21 plates and 7 tables. Edinburgh: E. & S. Livingstone, 1952. $8.00.

Synovial Fluid Changes in Joint Disease. By Marian W. Ropes, M.D., associate physician, Massachusetts General Hospital, and assistant clinical professor of medicine, Harvard Medical School; and Walter Bauer, M.D., chief of Medical Services, Massachusetts General Hospital, Jackson Professor of Clinical Medicine and director of Robert W. Lovett Memorial Foundation for the Study of Crippling Disease, Harvard Medical School. 8°, cloth, 150 pp., with 15 illustrations and 14 tables. Cambridge: Harvard University Press, 1953. $4.00.

Prescription for Rebellion. By Robert Lindner. 8°, cloth, 305 pp. New York: Rinehart and Company, Incorporated, 1952. $3.50.

The Superego: Unconscious conscience - the key to the theory and therapy of neurosis. By Edmund Bergler, M.D. 8°, cloth, 367 pp. New York: Grune and Stratton, 1952. $6.75.

New Outlook on Mental Diseases. By F. A. Pickworth, M.B., S.B., consultant pathologist, Group 6 Hospitals, Birmingham. 4°, cloth, 296 pp., with 41 illustrations. Baltimore: Williams and Wilkins, 1952. $12.00.

Handbook of Gynaecological Diagnosis for Practitioners and Students. By Walter Neuweiler, M.D., professor of midwifery and gynecology and director of the Gynaecological and Obstetrical Clinic in the University of Berne. Translated from the German by Dr. Paul Ederer. 8°, cloth, 448 pp., with 406 illustrations. New York: Grune and Stratton, 1952. $12.00.

This Is Your World: A book for the orientation of professional workers to the emotional problems of the chronically ill patient; tuberculosis and the individual. Written and illustrated by Harry A. Wilmer, M.D., Ph.D., consultant in psychiatry, San Mateo County Tuberculosis Sanatorium, instructor in medicine (neuropsychiatry), Stanford University School of Medicine, and consultant to Division of Chronic Disease and Tuberculosis, United States Public Health Service. With a foreword by Adelaide McF. Johnson, M.D., Ph.D., consultant in psychiatry, Mayo Clinic, associate professor of psychiatry, University of Minnesota Medical School, and member, Chicago Psychoanalytic Institute. 8°, cloth, 165 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.50. (Publication No. 140, *American Lecture Series.*)

Gynecology: Diseases and minor surgery. Compiled and edited by Robert J. Lowrie, M. A., M.D., D-OG, associate clinical professor of obstetrics and gynecology, New York University College of Medicine, attending gynecologist and obstetrician, St. Vincent's Hospital, attending obstetrician, City Hospital, Welfare Island, and attending gynecologist, Willard Parker Hospital. With a foreword by Claude E. Heaton, M.D. 4°, cloth, 806 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $22.50.

Experimental Diagnostics of Drives. By Dr. Med. L. Szondi. Translated by Gertrude Aull, assistant professor of psychology, Wagner College, New York City. 4°, cloth, 220 pp., with 48 tables and 66 figures. New York: Grune and Stratton, 1952. $13.50.

Appraising Personality: The use of psychological tests in the practice of medicine. By Molly Harrower, Ph.D., research director, Court Intake Project, New York City Court of Domestic Relations, consultant in psychology, United States Army, and editor, *American Lecture Series in Psychology.* 8°, cloth, 197 pp., with 17 charts and 19 illustrations. New York: W. W. Norton and Company, 1952. $4.00.

Pain Sensations and Reactions. By James D. Hardy, Ph.D., associate professor of physiology, Cornell University Medical College; Harold G. Wolff, M.D., professor of medicine (neurology), Cornell University Medical College; and Helen Goodell, B.S., research fellow in medicine, Cornell University Medical College. With a foreword by Edwin G. Boring, Ph.D., professor of psychology, Harvard University. 8°, cloth, 435 pp., with 130 illustrations and 20 tables. Baltimore: Williams and Wilkins, 1952. $6.50.

The Mechanisms of Disease: A study of the autonomic nervous system, the endocrine system and the electrolytes in their relationship to clinical medicine. By Joseph Stambul, M.D., chief, Cardiovascular Department, Albert Einstein Medical Center (Eastern Division), and cardiologist, Deborah Sanatorium. With a foreword by George M. Piersol, M.D., professor of medicine, Graduate School of Medicine, University of Pennsylvania, and editor-in-chief, *Cyclopedia of Medicine.* 8°, cloth, 746 pp. New York: Froben Press, Incorporated, 1952. $15.00.

Annual Epidemiological and Vital Statistics, 1939-1946. Part II. *Cases of and Deaths from Notifiable Diseases.* F°, paper, 326 pp. Geneva, Switzerland: World Health Organization, 1952. $4.00.

A Study in Manic-depressive Psychosis: Clinical, social and genetic investigations. By Ake Stenstedt. 8°, paper, 11 pp., with 27 tables. Copenhagen: Ejnar Munksgaard, 1952. 20 Swedish Crowns. (*Acta Psychiatrica et Neurologica Scandinavica*, Supplement No. 79.)

Some Principles of Hand Surgery. By John J. Byrne, M.D., assistant professor of surgery, Boston University School of Medicine, and co-ordinator of surgery, Third (Boston University) Surgical Service, Boston City Hospital. 4°, paper, 21 pp. Dr. Byrne, in this synopsis, outlines the essentials of hand surgery, including infections, injuries, contractures, congenital deformities, tumors and vascular diseases. The text concludes with two pages of references.

Free and Unequal: The biological basis of individual liberty. By Roger K. Williams. 8°, cloth, 177 pp., with illustrations. Austin: University of Texas, 1953. $3.50.

Ophthalmic Plastic Surgery. By Sidney A. Fox, M.S. (Ophth.), M.D., assistant clinical professor of ophthalmology, New York University Post-Graduate Medical School, attending ophthalmologist, Goldwater Memorial and Bronx Veterans Administration hospitals, associate ophthalmologist, Hospital for Joint Diseases, and assistant surgeon ophthalmologist, Bellevue Hospital, New York City. 8°, cloth, 290 pp., with 133 illustrations. New York: Grune and Stratton, 1952. $15.00.

Group Psychotherapy: Studies in Methodology of research and therapy. Report of a group psychotherapy research project of the United States Veterans Administration. By Florence B. Powdermaker, Ph.D., M.D., responsible investigator; and Jerome D. Frank, Ph.D., M.D., principal assistant. 8°, cloth, 615 pp., with 32 tables and 7 charts. Cambridge: Harvard University Press, 1953. $6.50.

Child Development: The process of growing up in society. By William E. Martin and Celia Burns Stedler, University of Illinois. Under the editorship of Willard B. Spalding, Oregon State System of Higher Education. 8°, cloth, 519 pp., with illustrations. New York: Harcourt, Brace and Company, 1953. $6.50.

Direct Analysis: Selected papers. By John N. Rosen, M.D. 8°, cloth, 184 pp., with 1 table. New York: Grune and Stratton, 1953. $3.75.

Memórias do Instituto Oswaldo Cruz, Rio de Janeiro, Brasil. Março de 1952. Tomo 50. 4°, paper, 731 pp., with illustrations and plates. Rio de Janeiro: Serviço Gráfico do Instituto Brasileiro de Geografia e Estatística, 1952.

Sociedad de obstetricia y ginecologia de Venezuela. "Recopilacion bibliografica nacional." Homenaje a la "primera reunion nacional de obstetricia y ginecologia." 8°, paper, 135 pp. Caracas, Venezuela: Tipografía A.B.C., 1952.

NOTICES

ANNOUNCEMENT

Dr. Charles C. Lund announces the removal of his office from 20 Gloucester Street to 319 Longwood Avenue, Boston.

NEW ENGLAND PATHOLOGICAL SOCIETY

A meeting of the New England Pathological Society will be held at the Mallory Institute of Pathology, Boston City Hospital, on Thursday, September 17, at 4:00 p.m. and will be followed by a slide seminar at 7:45 p.m.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The first meeting of the New England Society of Anesthesiologists for the year will be held in Boston jointly with the Massachusetts Society of Anesthesiologists in the Jorlin Auditorium, New England Deaconess Hospital, on Friday, October 16.

PROGRAM

8:00 a.m.–12:00 m. Clinics in various hospitals in Boston.
12:00 m.–2:00 p.m. Lunch.
2:00–3:00 p.m. Anesthesia Mortality Committee. Presentation of cases.
3:00–3:45 p.m. Dr. John Bunker, Massachusetts General Hospital. Anesthesia for the Acutely Burned Patient.
3:45–4:30 p.m. Dr. Arthur Ogden, Boston City Hospital. Anesthesia for Surgery of the Acute Abdomen.
4:30–5:30 p.m. Cocktails.
5:30–7:00 p.m. Dinner.
7:00–7:30 p.m. Business meeting.
7:30–9:30 p.m. Dr. A. M. Dogliotti (guest speaker), professor of surgery, chief of surgical clinic, University of Turin.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

The Nineteenth Postgraduate Seminar in Neurology and Psychiatry will be held in two parts, as follows:

Review course in basic neurology and psychiatry under the auspices of the Metropolitan State Hospital and the Psychiatric Training Faculty of Massachusetts, Incorporated, consisting of thirty lectures, every Monday, 2:00 to 8:30 p.m., from October 5 to December 7, at the Metropolitan State Hospital. Microscopes should be taken to the seminars in neuropathology, October 5 to November 9. Applications for the seminar should be submitted before October 1 to Dr. William F. McLaughlin, superintendent, Metropolitan State Hospital, 475 Trapelo Road, Waltham, Massachusetts.

Course in child psychiatry (pediatric neuropsychiatry), consisting of eight seminars of two hours each, every Wednesday, 7:00 to 9:00 p.m., from October 7 to December 2, at the Walter E. Fernald State School. Individual sessions will be announced later. Applications should be submitted to Dr. Malcolm J. Farrell, Walter E. Fernald State School, Waverley, Massachusetts.

SPRINGFIELD HEALTH DEPARTMENT

The Springfield Health Department office has been moved from City Hall, and is now located at 1414 State Street, in the Health Department Hospital Building.

AWARDS FOR UNIVERSITY LECTURING AND ADVANCED RESEARCH, 1954–1955

The Committee on International Exchange of Persons of the Conference Board of Associated Research Councils announces awards for visiting lecturers, under the Fulbright Act (Public Law 584). Lectures may be given in English. The following fields of particular interest to physicians, are included: sociology, history of science, biology, epidemiology and surgical anesthesia.

Ten awards are announced for research scholars. Applications will be accepted in any field.

Application forms and information may be obtained from the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Avenue, Washington 25, D. C. Applications must be submitted not later than October 15, 1953.

MEDICAL RESEARCH FELLOWSHIPS

Applications are being accepted by the Division of Medical Sciences of the National Research Council for postdoctoral investigative careers. The following program is announced for 1954–1955:

Fellowships in cancer research awarded by the American Cancer Society for study in all branches of the biologic, chemical and physical sciences (citizens of the United States are eligible).

British-American exchange fellowships in cancer research awarded by the American Cancer Society to citizens of the United States for advanced study in Great Britain and by the British Empire Cancer Campaign to British subjects for research in the United States.

Fellowships in the medical sciences supported by the Rockefeller Foundation and Lilly Research Laboratories, for research in basic medical sciences (Rockefeller fellowships are open to citizens of the United States and Canada; Lilly fellowships are open only to citizens of the United States).

Fellowships in tuberculosis granted by the National Tuberculosis Association (citizens of the United States who are graduates of American schools are eligible).

Fellowships in radiologic (diagnostic) research supported by the James Picker Foundation (appointments are not limited to citizens of the United States).

Applications for any of these programs must be submitted before December 10, 1953. Information may be obtained from the Fellowship Office, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 8. Springfield Academy of Medicine. Speaker: Dr. Neil W. Swinton.
SEPTEMBER 15. South End Medical Club. Page 344, issue of August 20.
SEPTEMBER 17. New England Pathological Society. Notice above.
SEPTEMBER 23. Middlesex South District Medical Society. Page 260, issue of August 6.
SEPTEMBER 23. American Medical Writers' Association. Page 386, issue of August 27.

(*Notices concluded on page xvii*)